Current margin practice and effect on re-excision rates following the publication of the SSO-ASTRO consensus and ABS consensus guidelines

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Current margin practice and effect on re-excision rates following the publication of the SSO-ASTRO consensus and ABS consensus guidelines: a national prospective study of 2858 women undergoing breast conserving therapy in the UK and Ireland

Abstract

Introduction: In the United Kingdom (UK) and Ireland, there is a lack of consensus on minimum margin width in breast conserving therapy (BCT) despite evidence supporting narrow excision margins particularly in invasive disease. In response to the recently published Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) margin consensus ("no ink on tumour" for invasive and 2mm for ductal carcinoma in situ, DCIS) and the UK Association of Breast Surgery (ABS) consensus (1mm for invasive and DCIS), the National Margins Research Collaborative reports on current margin practice and infrastructure in the UK and Ireland and their impact on re-excision rates.

Methods: A trainee collaborative-led multicentre prospective study was conducted in the UK and Ireland between 1st February and 31st May 2016. Site collaborators submitted data to a secure online database on consecutive BCT patients and also on local infrastructure and policies. Data analysis was performed using SPSS (ver. 23).

Results: 79 sites participated in the data collection (75% screening units; average of 372 cancers annually, range 70-900; BCT in 67% cases). There is greater variation in accepted margin width for DCIS (53.2% units accept 1mm; 38% accept 2mm) than invasive disease (77.2% accept 1mm; 13.9% accept no ink on tumour). 99% use guidewires for localisation and 96% use specimen X-Ray for intraoperative margin assessment. Within the study period 2858 patients underwent BCT with a mean re-excision rate of 17.2% across units (range 0-41%). The re-excision rate would be reduced to 15% if all units applied the SSO-ASTRO consensus guidelines and to 14.8% if all units followed the ABS guideline (1mm for invasive and DCIS). 65% patients returned to theatre because of disease present at margin(s) while 35% were due to proximity of cancer to specimen margin.

Conclusion: This is the largest prospective dataset of patients undergoing BCT in the UK. Infrastructure data revealed large variation in accepted margin width despite current evidence. In contrast, there is uniformity in techniques to localise impalpable lesions and intraoperative margin assessment. In our study there was wide variation in individual unit re-excision rates resulting in a national rate of 17.2%. Altering unit policies to following either SSO-ASTRO or ABS guidelines would have minimal effect because most re-excisions are for involved margins rather than close margins. Current approaches to intraoperative margin assessment can be improved and include optimising pre-operative tumour size measurements, identifying patients at increased risk of margin re-excision and evaluating alternative methods of intraoperative margin assessment. Reduction in re-excision rates will have patient and healthcare cost benefits.

BACKGROUND

Breast cancer is common with 1 in 8 women affected in their lifetime{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "http://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/lifetime-risk#ref-2", "accessed" : { "date-parts" : [["2017", "4", "20"]] }, "author" : [{ "dropping-particle" : "", "family" : "Cancer Research UK", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "id" : "ITEM-1", "issued" : { "date-parts" : [["0"]] }, "title" : "Lifetime risk of cancer", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=aed5359d-b675-4692-bce0-e4d149e425f0"] }], "mendeley" : { "formattedCitation" : "¹", "plainTextFormattedCitation" : "1", "previouslyFormattedCitation" : "¹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}. This is a disease with a high public profile, a well-established screening programme, strong funding streams, and has seen advances in treatment backed by strong research. Examples of these advances over the past 30 years include the introduction of breast conserving therapy (BCT) and sentinel node biopsy{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1097/SLA.0b013e3181c0e92a", "ISBN" : "1528-1140 (Electronic)\\r0003-4932 (Linking)", "PMID" : "20195151", "abstract" : "OBJECTIVE: Sentinel node biopsy (SNB) is widely used to stage the axilla in breast cancer. We present 10-year follow-up of our single-institute trial designed to compare outcomes in patients who received no axillary dissection if the sentinel node was negative, with patients who received complete axillary dissection. METHODS: From March 1998 to December 1999, 516 patients with primary breast cancer up to 2 cm in pathologic diameter were randomized either to SNB plus complete axillary dissection (AD arm) or to SNB with axillary dissection only if the sentinel node contained metastases (SN arm). RESULTS: The 2 arms were well-balanced for number of sentinel nodes found, proportion of positive sentinel nodes, and all other tumor and patient characteristics. About 8 patients in the AD arm had false-negative SNs on histologic analysis: a similar number (8, 95% CI: 3-15) of patients with axillary involvement was expected in SN arm patients who did not receive axillary dissection; but only 2 cases of overt axillary metastasis occurred. There were 23 breast cancer-related events in the SN arm and 26 in the AD arm (log-rank, P =

0.52), while overall survival was greater in the SN arm (log-rank, P = 0.15). CONCLUSIONS: Preservation of healthy lymph nodes may have beneficial consequences. Axillary dissection should not be performed in breast cancer patients without first examining the sentinel node.", "author" : [{ "dropping-particle" : "", "family" : "Veronesi", "given" : "U", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Viale", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Paganelli", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zurrida", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luini", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Galimberti", "given" : "V", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Veronesi", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Intra", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Maisonneuve", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zucca", "given" : "F", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gatti", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mazzarol", "given" : "G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cicco", "given" : "C", "non-dropping-particle" : "De", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vezzoli", "given" : "D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Ann Surg", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2010"]] }, "page" : "595-600", "title" : "Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study", "type" : "article-journal", "volume" : "251" }, "uris" : ["http://www.mendeley.com/documents/?uuid=cd9425e9-1cf1-422f-b5e6-4037a609b0b9"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1016/S0140-6736(97)01004-0", "ISBN" : "01406736", "ISSN" : "01406736", "PMID" : "9217757", "abstract" : "Background. Axillary lymph-node dissection is an important staging procedure in the surgical treatment of breast cancer. However, early diagnosis has led to increasing numbers of dissections in which axillary nodes are free of disease. This raises questions about the need for the procedure.

We carried out a study to assess, first, whether a single axillary lymph node (sentinel node) initially receives malignant cells from a breast carcinoma and, second, whether a clear sentinel node reliably forecasts a disease-free axilla. Methods. In a consecutive series of 163 women with operable breast carcinoma, we injected microcolloidal particles of human serum albumin labelled with technetium-99m. This tracer was injected subdermally, close to the tumour site, on the day before surgery, and scintigraphic images of the axilla and breast were taken 10 min, 30 min, and 3 h later. A mark was placed on the skin over the site of the radioactive node (sentinel node). During breast surgery, a hand-held ??-ray detector probe was used to locate the sentinel node, and make possible its separate removal via a small axillary incision. Complete axillary lymphadenectomy was then done. The sentinel node was tagged separately from other nodes. Permanent sections of all removed nodes were prepared for pathological examination. Findings. From the sentinel node, we could accurately predict axillary lymph-node status in 156 (97.5%) of the 160 patients in whom a sentinel node was identified, and in all cases (45 patients) with tumours less than 1.5 cm in diameter. In 32 (38%) of the 85 cases with metastatic axillary nodes, the only positive node was the sentinel node. Interpretation. In the large majority of patients with breast cancer, lymphoscintigraphy and ??-probe-guided surgery can be used to locate the sentinel node in the axilla, and thereby provide important information about the status of axillary nodes. Patients without clinical involvement of the axilla should undergo sentinel-node biopsy routinely, and may be spared complete axillary dissection when the sentinel node is disease-free.", "author" : [{ "dropping-particle" : "", "family" : "Veronesi", "given" : "Umberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Paganelli", "given" : "Giovanni", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Galimberti", "given" : "Viviana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Viale", "given" : "Giuseppe", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zurrida", "given" : "Stefano", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bedoni", "given" : "Marilia", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Costa", "given" : "Alberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cicco", "given" : "Concetta", "non-dropping-particle" : "De", "parse-names" :

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woman-years in the tamoxifen group. In the full study population, there were significant improvements in the anastrozole group compared with the tamoxifen group for disease-free survival (hazard ratio [HR] 0??91, 95% CI 0??83-0??99; p=0??04), time to recurrence (0??84, 0??75-0??93; p=0??001), and time to distant recurrence (0??87, 0??77-0??99; p=0??03). For hormone-receptor-positive patients, the results were also significantly in favour of the anastrozole group for disease-free survival (HR 0??86, 95% CI 0??78-0??95; p=0??003), time to recurrence (0??79, 0??70-0??89; p=0??0002), and time to distant recurrence (0??85, 0??73-0??98; p=0??02). In hormone-receptor-positive patients, absolute differences in time to recurrence between anastrozole and tamoxifen increased over time (2??7% at 5 years and 4??3% at 10 years) and recurrence rates remained significantly lower on anastrozole than tamoxifen after treatment completion (HR 0??81, 95% CI 0??67-0??98; p=0??03), although the carryover benefit was smaller after 8 years. There was weak evidence of fewer deaths after recurrence with anastrozole compared with tamoxifen treatment in the hormone-receptor-positive subgroup (HR 0??87, 95% CI 0??74-1??02; p=0??09), but there was little differe\u2026", "author" : [{ "dropping-particle" : "", "family" : "Cuzick", "given" : "Jack", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sestak", "given" : "Ivana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Baum", "given" : "Michael", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Buzdar", "given" : "Aman", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Howell", "given" : "Anthony", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dowsett", "given" : "Mitch", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Forbes", "given" : "John F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "The Lancet Oncology", "id" : "ITEM-1", "issue" : "12", "issued" : { "date-parts" : [["2010"]] }, "page" : "1135-1141", "title" : "Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial", "type" : "article-journal", "volume" : "11" }, "uris" : ["http://www.mendeley.com/documents/?uuid=73b6d900-1447-4dec-a5b8-95c44dc5ed9e"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1586/14737140.7.5.627", "ISBN" : "1473-7140", "ISSN" : "1473-7140", "PMID" : "17492927", "abstract" : "As there is a risk for relapse in early breast cancer, especially at 1-

3 years post surgery, the need for adjuvant therapy is clear. In terms of disease-free survival, aromatase inhibitors have emerged as superior to tamoxifen for the adjuvant treatment of hormone-sensitive breast cancer in several Phase III clinical trials. Of these trials, the Breast International Group (BIG) 1-98 trial stands out as unique in design, as it is the only trial to address whether an aromatase inhibitor is more effective as initial adjuvant therapy or as sequential therapy with an aromatase inhibitor and tamoxifen in either order and in rigor of end points and safety evaluations. When compared with tamoxifen, letrozole has been shown to significantly reduce recurrence risk in the overall population by 19% and also significantly reduced recurrence risk in the patient subgroups at increased risk: node-positive and previously chemotherapy-treated patients. Letrozole is the only aromatase inhibitor to demonstrate a significant 27% reduction in the risk of distant metastases ($p = 0.001$) in the clinically relevant, hormone receptor-positive population in the initial adjuvant setting. Recent results also suggest that letrozole in particular reduces the risk of distant metastases early on after initial surgery for breast cancer. This is important, as early distant metastatic events compose the majority of early recurrences and are a well-recognized predictor of breast cancer death. Letrozole has been found to be well tolerated in the initial adjuvant treatment setting, and these data have been confirmed by long-term safety data from the monotherapy analysis in the BIG 1-98 study. Thus far, the results from the BIG 1-98 trial provide clear support for the use of letrozole in the initial adjuvant treatment of breast cancer. Future studies will provide the definitive answer to questions of which initial adjuvant therapy is superior (i.e., anastrozole or letrozole) and information as to the optimal treatment strategy (i.e., initial adjuvant aromatase inhibitor therapy or sequential adjuvant aromatase inhibitor therapy). \u00a9 2007 Future Drugs Ltd.", "author" : [{ "dropping-particle" : "", "family" : "Monnier", "given" : "A M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Expert Review of Anticancer Therapy", "id" : "ITEM-2", "issue" : "5", "issued" : { "date-parts" : [["2007"]] }, "page" : "627-634", "title" : "The breast international group 1-98 trial: Big results for women with hormone-sensitive early breast cancer", "type" : "article-journal", "volume" : "7" }, "uris" : ["http://www.mendeley.com/documents/?uuid=92db92c7-c28f-46f9-b6af-8ba86b461074"] }], "mendeley" : { "formattedCitation" : "^{4,5}", "plainTextFormattedCitation" : "4,5", "previouslyFormattedCitation" : "^{4,5}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-

citation.json" }}, the development of anti-HER2 therapy{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0140-6736(13)61094-6", "ISBN" : "1474-547X (Electronic)\\n0140-6736 (Linking)", "ISSN" : "01406736", "PMID" : "23871490", "abstract" : "Background Trastuzumab has established efficacy against breast cancer with overexpression or amplification of the HER2 oncogene. The standard of care is 1 year of adjuvant trastuzumab, but the optimum duration of treatment is unknown. We compared 2 years of treatment with trastuzumab with 1 year of treatment, and updated the comparison of 1 year of trastuzumab versus observation at a median follow-up of 8 years, for patients enrolled in the HERceptin Adjuvant (HERA) trial. Methods The HERA trial is an international, multicentre, randomised, open-label, phase 3 trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both in 5102 patients with HER2-positive early breast cancer. The primary endpoint was disease-free survival. The comparison of 2 years versus 1 year of trastuzumab treatment involved a landmark analysis of 3105 patients who were disease-free 12 months after randomisation to one of the trastuzumab groups, and was planned after observing at least 725 disease-free survival events. The updated intention-to-treat comparison of 1 year trastuzumab treatment versus observation alone in 3399 patients at a median follow-up of 8 years (range 0-10) is also reported. This study is registered with ClinicalTrials.gov, number NCT00045032. Findings We recorded 367 events of disease-free survival in 1552 patients in the 1 year group and 367 events in 1553 patients in the 2 year group (hazard ratio [HR] 0??99, 95% CI 0??85-1??14, p=0??86). Grade 3-4 adverse events and decreases in left ventricular ejection fraction during treatment were reported more frequently in the 2 year treatment group than in the 1 year group (342 [20??4%] vs 275 [16??3%] grade 3-4 adverse events, and 120 [7??2%] vs 69 [4??1%] decreases in left ventricular ejection fraction, respectively). HRs for a comparison of 1 year of trastuzumab treatment versus observation were 0??76 (95% CI 0??67-0??86, p<0??0001) for disease-free survival and 0??76 (0??65-0??88, p=0??0005) for overall survival, despite crossover of 884 (52%) patients from the observation group to trastuzumab therapy. Interpretation 2 years of adjuvant trastuzumab is not more effective than is 1 year of treatment for patients with HER2-positive early breast cancer. 1 year of treatment provides a significant disease-free and overall survival benefit compared with observation and remains the standard of care. Funding F Hoffmann-La Roche (Roche)\u2026", "author" : [{ "dropping-particle" : "",

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percent in trial N9831. CONCLUSIONS: Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer. (ClinicalTrials.gov numbers, NCT00004067 and NCT00005970.)", "author" : [{ "dropping-particle" : "", "family" : "Romond", "given" : "Edward H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Perez", "given" : "Edith a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bryant", "given" : "John", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Suman", "given" : "Vera J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Geyer", "given" : "Charles E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Davidson", "given" : "Nancy E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tan-Chiu", "given" : "Elizabeth", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Martino", "given" : "Silvana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Paik", "given" : "Soonmyung", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kaufman", "given" : "Peter a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Swain", "given" : "Sandra M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pisansky", "given" : "Thomas M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fehrenbacher", "given" : "Louis", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kutteh", "given" : "Leila a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vogel", "given" : "Victor G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Visscher", "given" : "Daniel W", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Yothers", "given" : "Greg", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jenkins", "given" : "Robert B", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Brown", "given" : "Ann M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "",

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combinations and regimens in the metastatic and adjuvant settings", "author" : [{ "dropping-particle" : "", "family" : "Baselga", "given" : "Jos\u00e9 M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Oncology", "id" : "ITEM-3", "issue" : "suppl 2", "issued" : { "date-parts" : [["2001"]] }, "page" : "14-21", "title" : "Herceptin alone or in combination with chemotherapy in the treatment of HER2-positive metastatic breast cancer: pivotal trials", "type" : "article-journal", "volume" : "61 Suppl 2" }, "uris" : ["http://www.mendeley.com/documents/?uuid=13b1240b-54c1-44f2-8a79-07e578eda08e"] }], "mendeley" : { "formattedCitation" : "^{6\u20138}", "plainTextFormattedCitation" : "6\u20138", "previouslyFormattedCitation" : "^{6\u20138}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**, taxane based chemotherapy**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.breastdis.2013.01.026", "ISBN" : "0140-6736", "ISSN" : "1043321X", "PMID" : "22152853", "abstract" : "Background: Moderate differences in efficacy between adjuvant chemotherapy regimens for breast cancer are plausible, and could affect treatment choices. We sought any such differences. Methods: We undertook individual-patient-data meta-analyses of the randomised trials comparing: any taxane-plus-anthracycline- based regimen versus the same, or more, non-taxane chemotherapy (n=44 000); one anthracycline-based regimen versus another (n=7000) or versus cyclophosphamide, methotrexate, and fluorouracil (CMF; n=18 000); and polychemotherapy versus no chemotherapy (n=32 000). The scheduled dosages of these three drugs and of the anthracyclines doxorubicin (A) and epirubicin (E) were used to define standard CMF, standard 4AC, and CAF and CEF. Log-rank breast cancer mortality rate ratios (RRs) are reported. Findings: In trials adding four separate cycles of a taxane to a fixed anthracycline-based control regimen, extending treatment duration, breast cancer mortality was reduced (RR 0??86, SE 0??04, two-sided significance [2p]=0??0005). In trials with four such extra cycles of a taxane counterbalanced in controls by extra cycles of other cytotoxic drugs, roughly doubling non-taxane dosage, there was no significant difference (RR 0??94, SE 0??06, 2p=0??33). Trials with CMF-treated controls showed that standard 4AC and standard CMF were equivalent (RR 0??98, SE 0??05, 2p=0??67), but that anthracycline-based regimens with substantially higher cumulative dosage than standard 4AC (eg, CAF or CEF) were superior to standard CMF (RR 0??78, SE 0??06, 2p=0??0004). Trials versus no

chemotherapy also suggested greater mortality reductions with CAF (RR 0??64, SE 0??09, 2p<0??0001) than with standard 4AC (RR 0??78, SE 0??09, 2p=0??01) or standard CMF (RR 0??76, SE 0??05, 2p<0??0001). In all meta-analyses involving taxane-based or anthracycline-based regimens, proportional risk reductions were little affected by age, nodal status, tumour diameter or differentiation (moderate or poor; few were well differentiated), oestrogen receptor status, or tamoxifen use. Hence, largely independently of age (up to at least 70 years) or the tumour characteristics currently available to us for the patients selected to be in these trials, some taxane-plus-anthracycline-based or higher-cumulative-dosage anthracycline-based regimens (not requiring stem cells) reduced breast cancer mortality by, on average, about one-third. 10-year overall mortality differences paralleled breast cancer mortality d\u2026", "author" : [{ "dropping-particle" : "", "family" : "Henderson", "given" : "I. C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Breast Diseases", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2013"]] }, "page" : "76-78", "title" : "Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials", "type" : "article", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b5419301-c886-42fa-8e0f-bf31a2972837"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1200/JCO.2006.06.5391", "ISBN" : "1527-7755 (Electronic)\\r0732-183X (Linking)", "ISSN" : "0732183X", "PMID" : "17135639", "abstract" : "The combination of doxorubicin and cyclophosphamide (AC) is a standard adjuvant chemotherapy regimen. Studies of docetaxel and cyclophosphamide (TC) in metastatic breast cancer (MBC) showed promise in MBC. In 1997, we initiated a randomized adjuvant trial of TC compared with standard-dose AC with a primary end point of disease-free survival (DFS).", "author" : [{ "dropping-particle" : "", "family" : "Jones", "given" : "Stephen E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Savin", "given" : "Michael A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Holmes", "given" : "Frankie Ann", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "O'Shaughnessy", "given" : "Joyce A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Blum", "given" : "Joanne L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vukelja", "given" : "Svetislava", "non-dropping-

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547X (Electronic)\\r0140-6736 (Linking)", "ISSN" : "01406736", "PMID" : "26211824", "abstract" : "Background Bisphosphonates have profound eff ects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefi ts of adjuvant bisphosphonate treatment in breast cancer.", "author" : [{ "dropping-particle" : "", "family" : "Breast Cancer Trialists", "given" : "Early", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Group", "given" : "Collaborative", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "The Lancet", "id" : "ITEM-1", "issue" : "15", "issued" : { "date-parts" : [["2015"]] }, "page" : "1-9", "title" : "Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials", "type" : "article-journal", "volume" : "6736" }, "uris" : ["http://www.mendeley.com/documents/?uuid=5b5a5a75-4fed-4074-87b1-55e8c3edf41d"] }], "mendeley" : { "formattedCitation" : "¹¹", "plainTextFormattedCitation" : "11", "previouslyFormattedCitation" : "¹¹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

Six randomized controlled trials with up to 20 years of follow-up data have demonstrated overall equivalence between BCT and mastectomy for early-stage breast cancer **{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "ISBN" : "1081-4442 (Print)", "ISSN" : "1081-4442 (Print)", "PMID" : "9072310", "abstract" : "BACKGROUND: The randomized trials comparing breast-conserving therapy (BCT), i.e., surgery and radiation to the breast, with mastectomy in early-stage breast cancer use a variety of protocols. Meta-analysis may assist in understanding the impact of these differences on survival. PURPOSE: To evaluate the possible variations of the relative efficacy of BCT and mastectomy in terms of overall survival according to tumor size, nodal status, and use of adjuvant radiation therapy. METHODS: The most recent published results and, where available, updated patient-level data from randomized controlled trials of BCT and mastectomy for early-stage breast cancer were combined in a meta-analysis using a random effects model. Pooled survival rates and odds ratios were generated according to subgroups of nodal status and tumor size. Five- and 10-year odds ratios were also determined according to adjuvant radiation protocol. RESULTS: The pooled odds ratio comparing 10-year survival for BCT and

mastectomy was 0.91. The odds ratios comparing the two treatment regimens were not significant after grouping according to tumor size and nodal status. When more than 50% of node-positive patients in both the mastectomy and BCT arms received adjuvant radiation, both arms had similar survival rates. When less than 50% of node-positive patients in both arms received adjuvant nodal radiation, the odds ratio was 0.69, and patients receiving BCT had a survival advantage. CONCLUSIONS: Patients allocated to BCT have survival rates at least as high as patients allocated to mastectomy. When all protocols were combined, nodal status and tumor size did not significantly alter the relative survival rates. However, under some conditions, particularly for node-positive patients, BCT may confer a relative survival advantage over mastectomy. In particular, mastectomy without adjuvant radiation appears to be inferior to BCT for node-positive patients.", "author" : [{ "dropping-particle" : "", "family" : "Morris", "given" : "A D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morris", "given" : "R D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wilson", "given" : "J F", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "White", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Steinberg", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Okunieff", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Arriagada", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Le", "given" : "M G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Blichert-Toft", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dongen", "given" : "J A", "non-dropping-particle" : "van", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer J Sci Am", "id" : "ITEM-1", "issued" : { "date-parts" : [["1997"]] }, "page" : "6-12", "title" : "Breast-conserving therapy vs mastectomy in early-stage breast cancer: a meta-analysis of 10-year survival", "type" : "article-journal", "volume" : "3" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ff580f0e-ab26-47da-afff-54249f8c72c0"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1002/cncr.11580", "ISBN" : "0008-543X (Print)\\n0008-543X (Linking)", "PMID" : "12910512", "abstract" : "BACKGROUND: Between 1979-1987, the National Cancer Institute conducted a randomized, prospective study of

mastectomy (MT) versus breast conservation therapy (BCT) in the treatment of patients with early-stage breast carcinoma. After a median potential follow-up of 18.4 years, the authors present the updated results. METHODS: After informed consent was obtained from each patient, 237 evaluable women with clinical AJCC Stage I and Stage II breast carcinoma were enrolled on an institutionally reviewed protocol and randomly assigned to undergo modified radical MT (116 patients) or BCT (121 patients), which was comprised of lumpectomy, axillary lymph node dissection, and radiation therapy. Negative surgical margins in the lumpectomy arm were not required. The 237 randomized patients were followed for a median potential follow-up of 18.4 years. The primary endpoints were overall survival and disease-free survival. RESULTS: At a median follow-up of 18.4 years, there was no detectable difference with regard to overall survival between patients treated with MT and those treated with BCT (58% vs. 54%; P = 0.67 overall). Twenty-seven women in the BCT arm (22%) experienced an in-breast event. After censoring in-breast events in the BCT arm that were salvaged successfully by MT, disease-free survival also was found to be statistically similar (67% in the MT arm vs. 63% in the BCT arm; P = 0.64 overall). There was no statistically significant difference with regard to contralateral breast carcinoma between the two treatment arms (P = 0.70). CONCLUSIONS: After nearly 20 years of follow-up, there was no detectable difference in overall survival or disease-free survival in patients with early-stage breast carcinoma who were treated with MT compared with those treated with BCT. For BCT patients, long-term in-breast failures continued to occur throughout the duration of follow-up. There was no statistically significant difference in the incidence of contralateral breast carcinoma between the two treatment groups.", "author" : [{ "dropping-particle" : "", "family" : "Poggi", "given" : "M M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Danforth", "given" : "D N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sciuto", "given" : "L C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Smith", "given" : "S L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Steinberg", "given" : "S M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liewehr", "given" : "D J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Menard", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" :

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"", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Guinebreti\u00e8re", "given" : "J. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dunant", "given" : "A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rochard", "given" : "F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tursz", "given" : "T.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of Oncology", "id" : "ITEM-3", "issue" : "11", "issued" : { "date-parts" : [["2003"]] }, "page" : "1617-1622", "title" : "Late local recurrences in a randomised trial comparing conservative treatment with total mastectomy in early breast cancer patients", "type" : "article-journal", "volume" : "14" }, "uris" : ["http://www.mendeley.com/documents/?uuid=acaaf879-6964-4f6f-89cf-c81736476b64"] }, { "id" : "ITEM-4", "itemData" : { "DOI" : "10.1080/02841860801971439", "ISBN" : "0284186080197", "ISSN" : "1651-226X", "PMID" : "18465335", "abstract" : "The main objective of the present study aims at comparing the long-term efficacy of breast conserving surgery (BCS) vs. mastectomy (M) based on a randomized design. The Danish Breast Cancer Cooperative Group (DBCG) conducted the trial (DBCG-82TM) from January 1983 to March 1989 recruiting 1154 patients with invasive breast carcinoma. Follow-up time ended 1(st) May 2006 with a median follow-up time of 19.6 years (time span 17.1-23.3 years). Eligibility criteria included a one-sided, unifocal, primary operable breast carcinoma, patient age below 70 years, probability of satisfactory cosmetic outcome with BCS, and no evidence of disseminated disease. The patients accrued were grouped into three subsets: correctly randomized, suspicion of randomization error, and declining randomization. The main analyses focus on the subgroup of 793 correctly randomized patients representing 70% of the complete series. 10-year recurrence free survival (RFS) and 20-year overall survival (OS) based on intent to treat did not reveal significant differences in outcome between breast conserving surgery vs. mastectomy, p=0.95 and p=0.10, respectively. Including the complete series comprising 1133 eligible patients based on treatment in fact given similarly no significant difference between surgical options could be traced in outcome of 10-year RFS and 20-year OS, p=0.94 and p=0.24, respectively. The pattern of recurrences as a first event in breast conservation vs. mastectomy did not differ significantly irrespective of site, p=0.27. Looking into the type of local relapse, viz., new primaries vs. true recurrences, it appeared that new primaries were significantly associated to BCS, while true

recurrences dominated among M treated patients (p<0.001). In conclusion, long-term data indicate that BCS in eligible patients proves as effective as mastectomy both regarding local tumour control, RFS and OS. Local failures as a first event consistent with new primaries are strongly associated with BCS, whereas true recurrence predominates after mastectomy.", "author" : [{ "dropping-particle" : "", "family" : "Blichert-Toft", "given" : "Mogens", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nielsen", "given" : "Maja", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "D\u00fcring", "given" : "Maria", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "M\u00f8ller", "given" : "Susanne", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rank", "given" : "Fritz", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Overgaard", "given" : "Marie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mouridsen", "given" : "Henning T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Acta Oncol", "id" : "ITEM-4", "issue" : "4", "issued" : { "date-parts" : [["2008"]] }, "page" : "672-81", "title" : "Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol.", "type" : "article-journal", "volume" : "47" }, "uris" : ["http://www.mendeley.com/documents/?uuid=10f1a4b0-de08-46ac-9ee8-5a60ccda5b39"] }, { "id" : "ITEM-5", "itemData" : { "ISBN" : "0027-8874", "ISSN" : "0027-8874", "PMID" : "10904087", "abstract" : "BACKGROUND: Breast-conserving therapy (BCT) has been shown to be as effective as mastectomy in the treatment of tumors 2 cm or smaller. However, evidence of its efficacy, over the long term, in patients with tumors larger than 2 cm is limited. From May 1980 to May 1986, the European Organization for Research and Treatment of Cancer carried out a randomized, multicenter trial comparing BCT with modified radical mastectomy for patients with tumors up to 5 cm. In this analysis, we investigated whether the treatments resulted in different overall survival, time to distant metastasis, or time to locoregional recurrence. METHODS: Of 868 eligible breast cancer patients randomly assigned to the BCT arm or to the modified radical mastectomy arm, 80% had a tumor of 2.1-5 cm. BCT comprised lumpectomy with an attempted margin of 1 cm of healthy tissue and complete axillary clearance, followed by radiotherapy to the breast and a

supplementary dose to the tumor bed. The median follow-up was 13.4 years. All P values are two-sided. RESULTS: At 10 years, there was no difference between the two groups in overall survival (66% for the mastectomy patients and 65% for the BCT patients; P =.11) or in their distant metastasis-free rates (66% for the mastectomy patients and 61% for the BCT patients; P =.24). The rate of locoregional recurrence (occurring before or at the same time as distant metastasis) at 10 years did show a statistically significant difference (12% of the mastectomy and 20% of the BCT patients; P =. 01). CONCLUSIONS: BCT and mastectomy demonstrate similar survival rates in a trial in which the great majority of the patients had stage II breast cancer Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial\\nEnglish 200012. Entry Week: 2000121", "author" : [{ "dropping-particle" : "", "family" : "Dongen", "given" : "J A", "non-dropping-particle" : "van", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of the National Cancer Institute", "id" : "ITEM-5", "issue" : "14", "issued" : { "date-parts" : [["2000"]] }, "page" : "1143-1150", "title" : "Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European organization for research and treatment of cancer 10801 trial 4606", "type" : "article-journal", "volume" : "92" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ac505db9-c427-4f82-a7d1-35034d10f8f3"] }, { "id" : "ITEM-6", "itemData" : { "DOI" : "10.1056/NEJMoa020128", "ISBN" : "1533-4406 (Electronic)\\r0028-4793 (Linking)", "ISSN" : "1533-4406", "PMID" : "12192016", "abstract" : "BACKGROUND: In 1976, we initiated a randomized trial to determine whether lumpectomy with or without radiation therapy was as effective as total mastectomy for the treatment of invasive breast cancer. METHODS: A total of 1851 women for whom follow-up data were available and nodal status was known underwent randomly assigned treatment consisting of total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation. Kaplan-Meier and cumulative-incidence estimates of the outcome were obtained. RESULTS: The cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3 percent in the women who underwent lumpectomy and breast irradiation, as compared with 39.2 percent in the women who underwent lumpectomy without irradiation (P<0.001). No significant differences were observed among the three groups of women with respect to disease-free survival, distant-disease-free survival, or overall survival. The hazard ratio for death among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P=0.51). The

hazard ratio for death among the women who underwent lumpectomy followed by breast irradiation, as compared with those who underwent total mastectomy, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P=0.74). Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the hazard ratio for death among the women who underwent postoperative breast irradiation, as compared with those who did not, was 0.91 (95 percent confidence interval, 0.77 to 1.06; P=0.23). Radiation therapy was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes. CONCLUSIONS: Lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained.", "author" : [{ "dropping-particle" : "", "family" : "Fisher", "given" : "Bernard", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Anderson", "given" : "Stewart", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bryant", "given" : "John", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Margolese", "given" : "Richard G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Deutsch", "given" : "Melvin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fisher", "given" : "Edwin R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jeong", "given" : "Jong-Hyeon", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wolmark", "given" : "Norman", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "N Engl J Med", "id" : "ITEM-6", "issue" : "16", "issued" : { "date-parts" : [["2002"]] }, "page" : "1233-1241", "title" : "Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer", "type" : "article-journal", "volume" : "347" }, "uris" : ["http://www.mendeley.com/documents/?uuid=929981ba-e9f9-4d35-aef7-9f7a173f6a69"] }, { "id" : "ITEM-7", "itemData" : { "DOI" : "10.1056/NEJMoa020989", "ISBN" : "1533-4406 (Electronic)\\n0028-4793 (Linking)", "ISSN" : "1533-4406", "PMID" : "12393819", "abstract" : "BACKGROUND We conducted 20 years of follow-up of women enrolled in a randomized trial to compare the efficacy of radical (Halsted) mastectomy with that of breast-conserving

surgery. METHODS From 1973 to 1980, 701 women with breast cancers measuring no more than 2 cm in diameter were randomly assigned to undergo radical mastectomy (349 patients) or breast-conserving surgery (quadrantectomy) followed by radiotherapy to the ipsilateral mammary tissue (352 patients). After 1976, patients in both groups who had positive axillary nodes also received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. RESULTS Thirty women in the group that underwent breast-conserving therapy had a recurrence of tumor in the same breast, whereas eight women in the radical-mastectomy group had local recurrences (P<0.001). The crude cumulative incidence of these events was 8.8 percent and 2.3 percent, respectively, after 20 years. In contrast, there was no significant difference between the two groups in the rates of contralateral-breast carcinomas, distant metastases, or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7 percent in the group that underwent breast-conserving surgery and 41.2 percent in the radical-mastectomy group (P=1.0). The respective rates of death from breast cancer were 26.1 percent and 24.3 percent (P=0.8). CONCLUSIONS The long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy. Breast-conserving surgery is therefore the treatment of choice for women with relatively small breast cancers.", "author" : [{ "dropping-particle" : "", "family" : "Veronesi", "given" : "Umberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cascinelli", "given" : "Natale", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mariani", "given" : "Luigi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Greco", "given" : "Marco", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saccozzi", "given" : "Roberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luini", "given" : "Alberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Aguilar", "given" : "Marisel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Marubini", "given" : "Ettore", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "The New England journal of medicine", "id" : "ITEM-7", "issue" : "16", "issued" : { "date-parts" : [["2002"]] }, "page" : "1227-32", "title" : "Twenty-year follow-up of a randomized study comparing breast-

conserving surgery with radical mastectomy for early breast cancer.", "type" : "article-journal", "volume" : "347" }, "uris" : ["http://www.mendeley.com/documents/?uuid=2411ba6b-9560-48ac-8235-bb3b4011e58f"] }], "mendeley" : { "formattedCitation" : "^{12\u201318}", "plainTextFormattedCitation" : "12\u201318", "previouslyFormattedCitation" : "^{12\u201318}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Breast conservation offers a number of advantages over mastectomy. Preservation of the breast has psychological benefits, helping patients cope with their diagnosis and treatment**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1111/j.1075-122X.2004.21323.x", "ISSN" : "1075-122X", "PMID" : "15125749", "abstract" : "\u1b7f Abstract: There are many conflicting results in the literature comparing quality of life following breast-conserving therapy (BCT) and mastectomy. This study compared long-term quality of life between breast cancer patients treated by BCT or mastectomy in three age groups. Patients (n = 990) completed a quality of life survey, including the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), at regular intervals over 5 years. In the cross-sectional data, mastectomy patients had significantly ($p < 0.01$) lower body image, role, and sexual functioning scores and their lives were more disrupted than BCT patients. Emotional and social functioning and financial and future health worries were significantly ($p < 0.01$) worse for younger patients. There were no differences in body image and lifestyle scores between age groups. There was also no interaction between age and surgery method. Even patients \u2265 70 years of age reported higher body image and lifestyle scores when treated with BCT. The repeated measures analysis indicated that four functioning scores, half the symptom scores, future health, and global quality of life improved significantly ($p < 0.01$) over time. All these variables increased significantly for BCT patients and those 50 to 69 years of age. Body image, sexual functioning, and lifestyle disruption scores did not improve over time. BCT should be encouraged in all age groups. Coping with appearance change should be addressed in patient interventions. \u1b7f", "author" : [{ "dropping-particle" : "", "family" : "Engel", "given" : "Jutta", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kerr", "given" : "Jacqueline", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-

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surgery, simple mastectomy and breast reconstruction", "type" : "article-journal", "volume" : "36" }, "uris" : ["http://www.mendeley.com/documents/?uuid=4e396e8a-869c-447b-b01b-44b9c94acaef"] }], "mendeley" : { "formattedCitation" : "^{19,20}", "plainTextFormattedCitation" : "19,20", "previouslyFormattedCitation" : "^{19,20}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Additional benefits can include shorter operative and anaesthetic times, less post-operative discomfort and a reduced likelihood of clinically significant post-operative complications (e.g. haematoma, seroma**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1186/1477-7819-2-44", "ISBN" : "1477-7819 (Electronic)\\r1477-7819 (Linking)", "ISSN" : "14777819", "PMID" : "15588301", "abstract" : "Seroma formation is the most frequent postoperative complication after breast cancer surgery. We carried out a study to investigate the effect of various demographic, clinical and therapeutic variables on seroma formation. A retrospective cross sectional study of patients who underwent surgical therapy for breast cancer with either modified radical mastectomy (MRM) or breast preservation (BP) was carried out. The demographic data and clinical information were extracted from case records. Seroma formation was studied in relation to age, type of surgery, tumor size, nodal involvement, preoperative chemotherapy, surgical instrument (electrocautery or scalpel), use of pressure garment, and duration of drainage. The multiple logistic regression analysis was performed to estimate odds ratios. A total of 158 patients with breast cancer were studied. The mean age of the patients was 46.3 years (SD \u00b1 11.9). Seventy-three percent underwent modified radical mastectomy and the remaining 27% received breast preservation surgery. Seroma occurred in 35% of patients. In multivariate logistic regression analysis an association of postoperative seroma formation was noted with modified radical mastectomy (OR = 2.83, 95% CI 1.01\u20137.90, P = 0.04). No other factor studied was found to significantly effect the seroma formation after breast cancer surgery. The findings suggest that the type of surgery is a predicting factor for seroma formation in breast cancer patients.", "author" : [{ "dropping-particle" : "", "family" : "Hashemi", "given" : "Esmat", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kaviani", "given" : "Ahmad", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Najafi", "given" : "Masoume", "non-dropping-particle" : "", "parse-names" : false, "suffix" :

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rate was compared to the age of the patient, the presence and number of positive axillary lymph nodes, the total number of axillary lymph nodes removed, tumor size, weight of the patient, the use of neoadjuvant chemotherapy, and the type of surgery performed. The overall seroma rate was 15.8%. Seromas occurred in 19.9% of patients undergoing MRM and in 9.2% of patients undergoing breast-conserving surgery (p=0.01). The seroma rate was not influenced by any other tested variables. All seromas were easily managed with aspiration and pressure; this technical maneuver allowed seroma resolution in all patients except one following one to six aspirations. A seroma did not delay initiation of chemotherapy. No patient developed a capsule requiring excision. In our experience, a seroma is a \"necessary evil;\" it will occur unpredictably in a predictable number of patients.", "author" : [{ "dropping-particle" : "", "family" : "Gonzalez", "given" : "E A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saltzstein", "given" : "E C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Riedner", "given" : "C S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nelson", "given" : "B K", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Breast J", "id" : "ITEM-2", "issued" : { "date-parts" : [["2003"]] }, "page" : "385-388", "title" : "Seroma formation following breast cancer surgery", "type" : "article-journal", "volume" : "9" }, "uris" : ["http://www.mendeley.com/documents/?uuid=1f96703b-acb2-4054-8997-b6199f562954"] }], "mendeley" : { "formattedCitation" : "^{21,22}", "plainTextFormattedCitation" : "21,22", "previouslyFormattedCitation" : "^{21,22}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**). In the UK, day case wide local excision is supported by best practice tariffs. Shorter recovery with earlier return to work, particularly when compared to mastectomy with immediate reconstruction, has economic benefits for patients. For the majority of patients in whom wide local excision is technically and oncologically feasible, the cosmetic outcome is superior to what can be achieved by mastectomy and reconstruction**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1111/j.1075-122X.2004.21323.x", "ISSN" : "1075-122X", "PMID" : "15125749", "abstract" : "\u1b7f Abstract: There are many conflicting results in the literature comparing quality of life following breast-conserving therapy (BCT) and

mastectomy. This study compared long-term quality of life between breast cancer patients treated by BCT or mastectomy in three age groups. Patients (n = 990) completed a quality of life survey, including the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), at regular intervals over 5 years. In the cross-sectional data, mastectomy patients had significantly ($p < 0.01$) lower body image, role, and sexual functioning scores and their lives were more disrupted than BCT patients. Emotional and social functioning and financial and future health worries were significantly ($p < 0.01$) worse for younger patients. There were no differences in body image and lifestyle scores between age groups. There was also no interaction between age and surgery method. Even patients \u2265 70 years of age reported higher body image and lifestyle scores when treated with BCT. The repeated measures analysis indicated that four functioning scores, half the symptom scores, future health, and global quality of life improved significantly ($p < 0.01$) over time. All these variables increased significantly for BCT patients and those 50 to 69 years of age. Body image, sexual functioning, and lifestyle disruption scores did not improve over time. BCT should be encouraged in all age groups. Coping with appearance change should be addressed in patient interventions. \u1b7f", "author" : [{ "dropping-particle" : "", "family" : "Engel", "given" : "Jutta", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kerr", "given" : "Jacqueline", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schlesinger-Raab", "given" : "Anne", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sauer", "given" : "Hansj\u00f6rg", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "H\u00f6lzel", "given" : "Dieter", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "The Breast Journal", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2004"]] }, "page" : "223-231", "title" : "Quality of Life Following Breast-Conserving Therapy or Mastectomy: Results of a 5-Year Prospective Study", "type" : "article-journal", "volume" : "10" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e02c0541-f2ce-4d5c-84a8-d51e1dede2a3"] }], "mendeley" : { "formattedCitation" : "¹⁹", "plainTextFormattedCitation" : "19", "previouslyFormattedCitation" : "¹⁹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

Local control in BCT is largely attributed to 3 factors: clear resection margins, adjuvant radiotherapy and systemic therapy. Radiotherapy to the remaining breast has been shown to reduce local recurrence by 19%{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0140-6736(05)67887-7", "ISBN" : "0140-6736", "ISSN" : "01406736", "PMID" : "16360786", "abstract" : "Background: In early breast cancer, variations in local treatment that substantially affect the risk of locoregional recurrence could also affect long-term breast cancer mortality. To examine this relationship, collaborative meta-analyses were undertaken, based on individual patient data, of the relevant randomised trials that began by 1995. Methods: Information was available on 42 000 women in 78 randomised treatment comparisons (radiotherapy vs no radiotherapy, 23 500; more vs less surgery, 9300; more surgery vs radiotherapy, 9300). 24 types of local treatment comparison were identified. To help relate the effect on local (ie, locoregional) recurrence to that on breast cancer mortality, these were grouped according to whether or not the 5-year local recurrence risk exceeded 10% (<10%, 17 000 women; >10%, 25 000 women). Findings: About three-quarters of the eventual local recurrence risk occurred during the first 5 years. In the comparisons that involved little (<10%) difference in 5-year local recurrence risk there was little difference in 15-year breast cancer mortality. Among the 25 000 women in the comparisons that involved substantial (>10%) differences, however, 5-year local recurrence risks were 7% active versus 26% control (absolute reduction 19%), and 15-year breast cancer mortality risks were 44.6% versus 49.5% (absolute reduction 5.0%, SE 0.8, 2p<0.00001). These 25 000 women included 7300 with breast-conserving surgery (BCS) in trials of radiotherapy (generally just to the conserved breast), with 5-year local recurrence risks (mainly in the conserved breast, as most had axillary clearance and node-negative disease) 7% versus 26% (reduction 19%), and 15-year breast cancer mortality risks 30.5% versus 35.9% (reduction 5.4%, SE 1.7, 2p=0.0002; overall mortality reduction 5.3%, SE 1.8, 2p=0.005). They also included 8500 with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy (generally to the chest wall and regional lymph nodes), with similar absolute gains from radiotherapy; 5-year local recurrence risks (mainly at these sites) 6% versus 23% (reduction 17%), and 15-year breast cancer mortality risks 54.7% versus 60.1% (reduction 5.4%, SE 1.3, 2p=0.0002; overall mortality reduction 4.4%, SE 1.2, 2p=0.0009). Radiotherapy produced similar proportional

reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with \u2026", "author" : [{ "dropping-particle" : "", "family" : "Abe", "given" : "O.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Abe", "given" : "R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Enomoto", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kikuchi", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Koyama", "given" : "H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Masuda", "given" : "H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nomura", "given" : "Y.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sakai", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sugimachi", "given" : "K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tominaga", "given" : "T.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Uchino", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Yoshida", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Haybittle", "given" : "J. L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Davies", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harvey", "given" : "V. J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Holdaway", "given" : "T. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kay", "given" : "R. G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mason", "given" : "B. H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Forbes", "given" : "J. F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wilcken", "given" : "N.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gnant", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle"

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of the drug were combined. Patients who were not reassigned to either tamoxifen or placebo continued to be followed in the study. Survival, disease-free survival, and distant disease-free survival (relating to failure at distant sites) were estimated by use of the Kaplan-Meier method; differences between the treatment groups were assessed by use of the logrank test. The relative risks of failure (with 95% confidence intervals [CIs]) were determined by use of the Cox proportional hazards model. Reported P values are two-sided. RESULTS: Through 10 years of follow-up, a significant advantage in disease-free survival (69% versus 57%, P < .0001; relative risk = 0.66; 95% CI = 0.58-0.74), distant disease-free survival (76% versus 67%, P < .0001; relative risk = 0.70; 95% CI = 0.61-0.81), and survival (80% versus 76\u2026", "author" : [{ "dropping-particle" : "", "family" : "Fisher", "given" : "B", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dignam", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bryant", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "DeCillis", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wickerham", "given" : "D L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wolmark", "given" : "N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Costantino", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Redmond", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fisher", "given" : "E R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bowman", "given" : "D M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Desch\u00eanes", "given" : "L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "V", "family" : "Dimitrov", "given" : "N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Margolese", "given" : "R G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Robidoux", "given" : "a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Shibata", "given" : "H", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Terz", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-

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increased, adjusting for follow-up time [model 1: 1 mm (OR 1.0, referent), 2 mm (OR 0.95), 5 mm (OR 0.65), P = 0.21 for trend; and model 2: 1 mm (OR 1.0, referent), 2 mm (OR 0.91), 5 mm (OR 0.77), P = 0.58 for trend]. Adjustment for covariates, such as use of endocrine therapy or median-year of recruitment, did not change the findings. Conclusions: Meta-analysis confirms that negative margins reduce the odds of LR; however, increasing the distance for defining negative margins is not significantly associated with reduced odds of LR, allowing for follow-up time. Adoption of wider relative to narrower margin widths to declare negative margins is unlikely to have a substantial additional benefit for long-term local control in BCT. \u00a9 2014 Society of Surgical Oncology.", "author" : [{ "dropping-particle" : "", "family" : "Houssami", "given" : "Nehmat", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Macaskill", "given" : "Petra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luke Marinovich", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morrow", "given" : "Monica", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of Surgical Oncology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "717-730", "title" : "The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis", "type" : "article-journal", "volume" : "21" }, "uris" : ["http://www.mendeley.com/documents/?uuid=db62836c-3d64-49df-8f72-aa33c7d56cff"] }], "mendeley" : { "formattedCitation" : "²⁶", "plainTextFormattedCitation" : "26", "previouslyFormattedCitation" : "²⁶" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. This study found that local recurrence is more than twice as likely with positive margins compared to negative margins (odds ratio 2.44). However, as long as there was no ink on tumour, wider margins did not significantly alter the local recurrence rate. Importantly, this finding was also true in unfavourable cases such as in younger patients, those with more aggressive tumour biology, lobular cancers or those with an extensive intraductal component. In 2014, SSO-ASTRO published their consensus guideline recommending the use of “no ink on tumour” as the standard for adequate margin in invasive breast cancer**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "author" : [{ "dropping-particle" : "", "family" : "Moran", "given" : "Meena S.",

"non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schnitt", "given" : "Stuart J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Giuliano", "given" : "A.E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harris", "given" : "J. R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Khan", "given" : "S.A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Horton", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Klimberg", "given" : "S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chavez-MacGregor", "given" : "Mariana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Freedman", "given" : "G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Houssami", "given" : "Nehmat", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Johnson", "given" : "P.L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morrow", "given" : "Monica", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Ann Surg Oncol", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "704-16", "title" : "Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer", "type" : "article-journal", "volume" : "21" }, "uris" : ["http://www.mendeley.com/documents/?uuid=0817464e-9ebe-49d4-839b-43d3775fc775"] }], "mendeley" : { "formattedCitation" : "²⁷", "plainTextFormattedCitation" : "27", "previouslyFormattedCitation" : "²⁷" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. In 2015, ABS published its consensus statement for margins in BCT recommending 1mm for invasive disease and 1mm for DCIS**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "abstract" : "1. ABS advises a one millimetre (1mm) minimum clear radial margin is achieved after breast conservation surgery for early invasive breast cancer 2. ABS advises a one millimetre (1mm) minimum clear radial margin is achieved after breast conservation surgery for in situ carcinoma of the breast At the ABS Conference & AGM in Bournemouth on 15 th June 2015

a session was devoted to a discussion on what should be the most appropriate advice on the minimum acceptable margin after breast conservation surgery in early breast cancer. Talks were given on current UK-based guidelines, the histopathological process of margin determination, literature reviews on the relevant margin evidence for both invasive and in situ disease and practice and guidelines adopted in other countries. 370 voter key pads were available. 61% of the voters were consultant breast surgeons, 24% non-consultant breast surgeons, 6% breast care nurses and the remainder were consultants from other disciplines and allied health professionals. Motions were proposed and voted on. The first motion was \" The ABS advises a one millimetre minimum clear radial margin is achieved after breast conservation surgery for early invasive breast cancer \" . \uf0b7 88% voted in favour \uf0b7 12% voted against. Voting breakdown showed that 88% of the consultant breast surgeons voted in favour of the motion. The second motion was \" The ABS advises a one millimetre minimum clear radial margin is achieved after breast conservation surgery for in situ carcinoma of the breast. \" \uf0b7 69% voted in favour \uf0b7 31% voted against. Voting breakdown showed that 69% of the consultant breast surgeons voted in favour as did 80% of the specialist surgical trainees. 50% of trust doctors and 34% of breast care nurses voted against.", "id" : "ITEM-1", "issued" : { "date-parts" : [["2015"]] }, "title" : "Association of Breast Surgery ABS Consensus Margin Width in Breast Conservation Surgery", "type" : "paper-conference" }, "uris" : ["http://www.mendeley.com/documents/?uuid=43d5ea73-d7b1-4bc1-a5ee-d8c5a562a580"] }], "mendeley" : { "formattedCitation" : "²⁸", "plainTextFormattedCitation" : "28", "previouslyFormattedCitation" : "²⁸" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. In 2016, SSO-ASTRO-ASCO published a meta-analysis on margin width and local recurrence in DCIS, resulting in its consensus guideline of 2mm for DCIS**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.prro.2016.06.011", "ISBN" : "1879-355X (Electronic)\\r0360-3016 (Linking)", "ISSN" : "18798500", "PMID" : "27528719", "abstract" : "Purpose Controversy exists regarding the optimal negative margin width for ductal carcinoma in situ (DCIS) treated with breast-conserving surgery and whole-breast irradiation. Methods and materials A multidisciplinary consensus panel used a meta-analysis of margin width and ipsilateral breast tumor recurrence (IBTR) from a systematic review of 20 studies including 7883

patients and other published literature as the evidence base for consensus. Results Negative margins halve the risk of IBTR compared with positive margins defined as ink on DCIS. A 2-mm margin minimizes the risk of IBTR compared with smaller negative margins. More widely clear margins do not significantly decrease IBTR compared with 2-mm margins. Negative margins narrower than 2 mm alone are not an indication for mastectomy, and factors known to affect rates of IBTR should be considered in determining the need for re-excision. Conclusion Use of a 2-mm margin as the standard for an adequate margin in DCIS treated with whole-breast irradiation is associated with lower rates of IBTR and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs. Clinical judgment should be used in determining the need for further surgery in patients with negative margins narrower than 2 mm.", "author" : [{ "dropping-particle" : "", "family" : "Morrow", "given" : "Monica", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Zee", "given" : "Kimberly J.", "non-dropping-particle" : "Van", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Solin", "given" : "Lawrence J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Houssami", "given" : "Nehmat", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Chavez-MacGregor", "given" : "Mariana", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harris", "given" : "Jay R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Horton", "given" : "Janet", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hwang", "given" : "Shelley", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Johnson", "given" : "Peggy L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Marinovich", "given" : "M. Luke", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Schnitt", "given" : "Stuart J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wapnir", "given" : "Irene", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Moran", "given" : "Meena S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Practical Radiation Oncology", "id" : "ITEM-1", "issue" : "5", "issued" : { "date-parts" : [["2016"]] }, "page" : "287-295", "title" : "Society of Surgical

Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ", "type" : "article-journal", "volume" : "6" }, "uris" : ["http://www.mendeley.com/documents/?uuid=02ae3e81-a1cc-448c-b91b-22a45d296afe"] }], "mendeley" : { "formattedCitation" : "²⁹", "plainTextFormattedCitation" : "29", "previouslyFormattedCitation" : "²⁹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

Despite an increasing body of evidence supporting narrow margins in BCT, there is still a lack of consensus in margin policy in the UK. In addition to the international guidelines published recently, national and regional guidelines are also available and include guidance from the National Institute for Health and Care Excellence (NICE) which defines a margin clearance of 2mm for DCIS**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "id" : "ITEM-1", "issued" : { "date-parts" : [["2009"]] }, "title" : "Early and locally advanced breast cancer: diagnosis and treatment. NICE guideline (CG80).", "type" : "report" }, "uris" : ["http://www.mendeley.com/documents/?uuid=13a1305c-081f-4ac5-86d4-d8fcdee015f5"] }], "mendeley" : { "formattedCitation" : "³⁰", "plainTextFormattedCitation" : "30", "previouslyFormattedCitation" : "³⁰" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. This lack of consensus is confusing for UK breast clinicians and variation in margin policy may result in unequal care with some patients undergoing unnecessary additional surgery. Pursuing excessively wide margins has a number of detrimental effects. Resection of larger volumes of tissue may have a cosmetic impact that can be further exacerbated by radiotherapy, and may require additional procedures such as lipomodelling increasing healthcare costs. Patients undergoing margin re-excision experience additional emotional stress, a greater risk of wound infection**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1245/s10434-014-4200-x", "ISSN" : "1534-4681", "PMID" : "25358666", "abstract" : "PURPOSE: The aim of this study was to determine the risk of surgical site infection (SSI) after primary breast-conserving surgery (BCS) versus re-excision among women with carcinoma in situ or invasive breast cancer.\\n\\nMETHODS: We established a retrospective cohort of women aged 18-64 years with International

Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure or Current Procedural Terminology, 4th edition (CPT-4) codes for BCS from 29 June 2004 to 31 December 2010. Prior insurance plan enrollment of at least 180 days was required to establish the index BCS; subsequent re-excisions within 180 days were identified. SSIs occurring 2-90 days after BCS were identified by ICD-9-CM diagnosis codes. The attributable surgery was defined based on SSI onset compared with the BCS date(s). A \u03c7 (2) test and generalized estimating equations model were used to compare the incidence of SSI after index and re-excision BCS procedures.\\n\\nRESULTS: Overall, 23,001 women with 28,827 BCSs were identified; 23.2 % of women had more than one BCS. The incidence of SSI was 1.82 % (418/23,001) for the index BCS and 2.44 % (142/5,826) for re-excision BCS (p = 0.002). The risk of SSI after re-excision remained significantly higher after accounting for multiple procedures within a woman (odds ratio 1.34, 95 % confidence interval 1.07-1.68).\\n\\nCONCLUSIONS: Surgeons need to be aware of the increased risk of SSI after re-excision BCS compared with the initial procedure. Our results suggest that risk adjustment of SSI rates for re-excision would allow for better comparison of BCS SSI rates between institutions.", "author" : [{ "dropping-particle" : "", "family" : "Olsen", "given" : "Margaret a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nickel", "given" : "Katelin B", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Margenthaler", "given" : "Julie a", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wallace", "given" : "Anna E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mines", "given" : "Daniel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Miller", "given" : "J Philip", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fraser", "given" : "Victoria J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Warren", "given" : "David K", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of surgical oncology", "id" : "ITEM-1", "issue" : "6", "issued" : { "date-parts" : [["2015"]] }, "page" : "2003-9", "title" : "Increased Risk of Surgical Site Infection Among Breast-Conserving Surgery Re-excisions.", "type" : "article-journal", "volume" : "22" }, "uris" : ["http://www.mendeley.com/documents/?uuid=c0ceb51e-2fd6-4d1a-8487-76ada0a9ad46"] }], "mendeley" : { "formattedCitation" : "³¹",

"plainTextFormattedCitation" : "31", "previouslyFormattedCitation" : "³¹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**, increased scarring and further general anaesthetic. A larger retrospective study of BCT in England using hospital episode statistics found an overall re-operation rate of 20% with substantial differences in the rates between NHS Trusts (10th and 90th centiles of 12.2% and 30.2%)**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1136/bmj.e4505", "ISBN" : "1756-1833 (Electronic)\\r0959-535X (Linking)", "ISSN" : "1756-1833", "PMID" : "22791786", "abstract" : "OBJECTIVES: To examine whether rate of reoperation after breast conserving surgery is associated with patients' characteristics and investigate whether reoperation rates vary among English NHS trusts.\\n\\nDESIGN: Cohort study using patient level data from hospital episode statistics.\\n\\nSETTING: English NHS trusts.\\n\\nPARTICIPANTS: Adult women who had breast conserving surgery between 1 April 2005 and 31 March 2008.\\n\\nMAIN OUTCOME MEASURE: Reoperation rates after primary breast conserving surgery within 3 months, adjusted using logistic regression for tumour type, age, comorbidity, and socioeconomic deprivation. Tumours were grouped by whether a carcinoma in situ component was coded at the time of the primary breast conserving surgery.\\n\\nRESULTS: 55,297 women had primary breast conserving surgery in 156 NHS trusts during the three year period. 11,032 (20.0%, 95% confidence interval 19.6% to 20.3%) women had at least one reoperation. 10,212 (18.5%, 18.2% to 18.8%) had one reoperation only; of these, 5943 (10.7%, 10.5% to 11.0%) had another breast conserving procedure and 4269 (7.7%, 7.5% to 7.9%) had a mastectomy. Of the 45,793 women with isolated invasive disease, 8229 (18.0%) had at least one reoperation. In comparison, 2803 (29.5%) of the 9504 women with carcinoma in situ had at least one reoperation (adjusted odds ratio 1.9, 95% confidence interval 1.8 to 2.0). Substantial differences were found in the adjusted reoperation rates among the NHS trusts (10th and 90th centiles 12.2% and 30.2%).\\n\\nCONCLUSION: One in five women who had breast conserving surgery in England had a reoperation. Reoperation was nearly twice as likely when the tumour had a carcinoma in situ component coded. Women should be informed of this reoperation risk when deciding on the type of surgical treatment of their breast cancer.", "author" : [{ "dropping-particle" : "", "family" : "Jeevan", "given" : "R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cromwell", "given"

: "D. A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Trivella", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lawrence", "given" : "G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kearins", "given" : "O.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pereira", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sheppard", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Caddy", "given" : "C. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Meulen", "given" : "J. H. P.", "non-dropping-particle" : "van der", "parse-names" : false, "suffix" : "" }], "container-title" : "BMJ", "id" : "ITEM-1", "issue" : "jul12 2", "issued" : { "date-parts" : [["2012"]] }, "page" : "e4505-e4505", "title" : "Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics", "type" : "article-journal", "volume" : "345" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8ab50923-cc06-49de-af70-cc578d25b7c4"] }], "mendeley" : { "formattedCitation" : "³²", "plainTextFormattedCitation" : "32", "previouslyFormattedCitation" : "³²" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Margin re-excision places an additional burden on already busy operating lists and may delay the onset of adjuvant treatments. Supplementary healthcare costs result from a second (or more) anaesthetic, a hospital bed and further histological analysis**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.jamcollsurg.2017.03.020", "ISSN" : "1072-7515", "author" : [{ "dropping-particle" : "", "family" : "Yu", "given" : "Jennifer", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Elmore", "given" : "Leisha C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cyr", "given" : "Amy E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Aft", "given" : "Rebecca L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gillanders", "given" : "William E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Margenthaler", "given" : "Julie A",

"non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of the American College of Surgeons", "id" : "ITEM-1", "issued" : { "date-parts" : [["2017", "4", "20"]] }, "note" : "doi: 10.1016/j.jamcollsurg.2017.03.020", "publisher" : "Elsevier", "title" : "Cost Analysis of a Surgical Consensus Guideline in Breast-Conserving Surgery", "type" : "article-journal" }, "uris" : ["http://www.mendeley.com/documents/?uuid=943552e4-406e-43c3-929b-b9869662d2d1"] }], "mendeley" : { "formattedCitation" : "³³", "plainTextFormattedCitation" : "33", "previouslyFormattedCitation" : "³³" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**.

Due to existing variation in practice in the UK, this prospective study was set up to evaluate the response to the recently published SSO-ASTRO and ABS guidelines. We aimed to describe current margin practice in breast units in the UK and Ireland and to examine the effect that margin policy and local infrastructure have on re-excision rates.

METHODS

All breast centres in the UK and Ireland were invited to participate in the study through a national campaign. A dedicated National Margins Audit project page was created on the London Surgical Research Group (LSRG) website through which the full study protocol could be downloaded**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "http://lsrg.org.uk/projects/national-margins-audit/", "accessed" : { "date-parts" : [["2017", "4", "20"]] }, "id" : "ITEM-1", "issued" : { "date-parts" : [["2016"]] }, "title" : "LONDON SURGICAL RESEARCH GROUP. National Margins Audit: A study looking at excision margins and outcomes in DCIS and invasive breast cancer [Online]. London: London Surgical Research Group.", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=9f21076b-2d18-442b-acca-26c96c337817"] }], "mendeley" : { "formattedCitation" : "³⁴", "plainTextFormattedCitation" : "34", "previouslyFormattedCitation" : "³⁴" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-

citation.json" }**}**. A trainee collaborative research method was used following the example of a number of successful trainee led research collaborative studies in breast and general surgery in the UK**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0140-6736(13)62013-9", "ISSN" : "01406736", "PMID" : "24075040", "abstract" : "Over the past 5 years, trainee-led regional networks in general surgery have been developed to adopt a novel collaborative approach to research in the UK. This approach allows for a larger number of patients to be included in less time, prevents repetition, and permits greater generalisability than single-centre studies. Trainees are ideally placed to deliver this model; they follow a rotational pattern through several hospitals, are in regular contact with each other, are motivated, and require formalised evidence of research and audit. As these trainees become consultants, a culture of trials could be distilled in UK surgical practice.\\nThe first regionally developed general surgical research collaborative was the West Midlands Research Collaborative. Their recently published randomised controlled trial, ROSSINI (Reduction Of Surgical Site Infection using a Novel Intervention),1 recruited 760 patients from 21 centres to use either a wound-edge protection device or standard practice. The rapid recruitment (the trial ran ahead of schedule throughout) and minimal loss to follow-up demonstrated the ability of trainees to plan and conduct high-quality multicentre research.\\nOther general surgical research collaboratives were subsequently established allowing for almost complete coverage of the UK. These regional networks recently delivered the Multicentre Appendicectomy Audit, including 3326 consecutive patients undergoing appendicectomy from 95 centres during 2 months.2 Further trainee-led randomised trials and national cohort studies developed from these groups are ongoing, and are recruiting patients across the UK. The ROCSS (Reinforcement of Closure of Stoma Site) study3 is an example of how trainee network can deliver a large randomised trial for a complex surgical intervention, while collaborating successfully with industry.\\nMore specialised surgical disciplines are centralised in tertiary units or large regional hospitals, and so require a national rather than regional network. Examples of trainee collaborative model include paediatric surgery, neurosurgery, plastic surgery, and cardiothoracic surgery. In June, 2013, the first national study from the British Neurosurgical Trainee Research Collaborative was launched: a prospective cohort study of patients with chronic subdural haematoma. Two randomised trials and a further prospective cohort study are currently in development.4 Cross-specialty collaboratives are now

developing in the UK following th\u2026", "author" : [{ "dropping-particle" : "", "family" : "Bhangu", "given" : "Aneel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kolias", "given" : "Angelos G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pinkney", "given" : "Thomas", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hall", "given" : "Nigel J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fitzgerald", "given" : "J. Edward", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "The Lancet", "id" : "ITEM-1", "issue" : "9898", "issued" : { "date-parts" : [["2013"]] }, "page" : "1091-1092", "title" : "Surgical research collaboratives in the UK", "type" : "article", "volume" : "382" }, "uris" : ["http://www.mendeley.com/documents/?uuid=4576efcc-c4a0-4a11-b071-c6df15056d86"] }], "mendeley" : { "formattedCitation" : "³⁵", "plainTextFormattedCitation" : "35", "previouslyFormattedCitation" : "³⁵" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. A lead trainee was identified at each site either through the network of trainee collaboratives led by the LSRG or were nominated by their unit consultant. Each unit obtained local audit approval. Investigators completed a questionnaire regarding their unit margin policies, as well as providing data on their number of surgeons and breast cancers treated, their screening status, the methods of localising non-palpable lesions and intraoperative margin assessment.

A national prospective study was undertaken from 1st February to 31st May 2016 on all consecutive patients undergoing wide local excision for DCIS and invasive carcinoma. An online REDCap database was created to capture this data and a server was set up by the information technology department at St George's University of London to store the data securely**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.jbi.2008.08.010.Research", "ISBN" : "1532-0480 (Electronic)\\n1532-0464 (Linking)", "ISSN" : "1532-0480", "PMID" : "18929686", "abstract" : "REDCap is a novel workflow methodology and software solution designed for rapid development and deployment of electronic data capture tools to support clinical and translational research. We present: 1) a brief description of the REDCap metadata-driven software toolset; 2) detail

concerning the capture and use of study-related metadata from scientific research teams; 3) measures of impact for REDCap; 4) details concerning a consortium network of domestic and international institutions collaborating on the project; and 5) strengths and limitations of the REDCap system. REDCap is currently supporting 286 translational research projects in a growing collaborative network including 27 active partner institutions.", "author" : [{ "dropping-particle" : "", "family" : "Harris", "given" : "Paul a.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Taylor", "given" : "Robert", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Thielke", "given" : "Robert", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Payne", "given" : "Jonathon", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gonzalez", "given" : "Nathaniel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Conde", "given" : "Jose G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of Biomedical Informatics", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2009"]] }, "page" : "377-81", "title" : "Research Electronic Data Capture (REDCap) - A metadata driven methodology and workflow process for providing translational research informatics support.", "type" : "article-journal", "volume" : "42" }, "uris" : ["http://www.mendeley.com/documents/?uuid=a2152330-e244-4271-8de8-81103620eceb"] }], "mendeley" : { "formattedCitation" : "³⁶", "plainTextFormattedCitation" : "36", "previouslyFormattedCitation" : "³⁶" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Access to the database was achieved via the entry of individualised passwords created for each investigator and all data entered into REDCap was stripped of patient identifiers. Each centre was allocated a unique identification code and investigators created a study ID for each patient using the centre ID as a pre-fix. Details of surgery were collected for each patient and included date of primary surgery, closest margin measurements, whether margins were considered involved, whether re-excision took place and details of subsequent re-operations (margin re-excision or mastectomy). Patients were followed up until the completion of their surgical treatment. Data analysis was performed using SPSS (ver. 23). Chi squared tests and ANOVA were used for categorical data and t-tests and Pearson correlation were used for parametric data. A two-sided 5% alpha level was

used to assess statistically significant differences. The study was reported according to STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) guidelines{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "https://strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_cohort.pdf", "accessed" : { "date-parts" : [["2017", "6", "1"]] }, "id" : "ITEM-1", "issued" : { "date-parts" : [["0"]] }, "title" : "STROBE checklist for cohort studies", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=1d9296db-c00d-431f-8f42-16d3036215e4"] }], "mendeley" : { "formattedCitation" : "³⁷", "plainTextFormattedCitation" : "37", "previouslyFormattedCitation" : "³⁷" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}.

RESULTS

Seventy-nine hospitals (approximately half of UK breast units) returned questionnaires describing their infrastructure and of these 76 contributed patient specific data. There was broad geographic representation of units in England and Wales with both teaching hospitals and district general hospitals contributing to the study (Figure 1). Four large breast units in Scotland (Edinburgh, Glasgow, Aberdeen, Dundee), three units in Northern Ireland (Antrim area, Ulster, Craigavon Area) and one unit in Ireland (Waterford) also participated.

Of these, 75% were screening units employing a mean of 3.29 consultant surgeons (range 1-10), 1.5 specialty doctors (range 0-5) and 1.76 trainees (range 0-8 trainees). A mean of 372 breast cancers are treated annually per site (range 70-900, median 342). In participating units, a mean of 67% of breast cancers treated by primary surgery undergo BCT (range 42-80%, median 70%). Responses are presented in detail in Table 1.

When asked which guidelines were followed for margins, some units selected more than one option. NICE guidelines for DCIS were followed by 22% of units while 48% followed the ABS consensus, 17% followed regional guidelines (see table 2) and 4% followed the ASCO

consensus guideline. Local discussion within multidisciplinary teams (MDT) was used to achieve a final consensus on margins in 40% of units.

MDT standards for adequate margins are presented in Table 3 (invasive disease) and Table 4 (DCIS). Only 13.9% of units have a “no ink on tumour” policy for invasive disease, while 77.2% accept a 1mm margin. For DCIS, 53.2% of units accept a 1mm margin and 38% accept a 2mm margin.

Ninety-nine percent of units use guidewires and 3.8% use Radioguided Occult Lesion Localisation (ROLL) to localise non-palpable lesions (Table 5). Intraoperative margin assessment was performed by specimen X-ray in 96% of units (Table 6). 87% of units only take cavity shaves after clinical and radiological assessment (Table 7). Ten units take four margin cavity shaves as standard practice for either some or all of the surgeons (describing normal practice for a total of 24 surgeons within the study).

Over the 4-month study period, data was collected on 2858 consecutive patients undergoing BCT. The number of cases per unit ranged from 11 to 119 patients. 493 patients underwent at least one further operation for margins giving a national re-excision rate of 17.2% with rates ranging from 0% to 41% (median 17%) in individual units (Figure 1). No relationship was found between number of cases performed by each unit (p=0.84), number of consultant surgeons (p=0.09), screening unit status (p=0.9), and the use of intraoperative specimen X-ray (p=0.4) and the margin re-excision. Higher re-excision rates were seen in units with more than one trainee (p=0.007).

Closest margin widths were recorded for all cases. If all participating breast units had followed SSO-ASTRO’s guidelines (“no ink on tumour” for invasive disease and greater than 2mm for DCIS), this would have resulted in 52 cases avoiding further surgery, resulting in a new national re-excision rate of 15.4% (p=0.07). If all breast units followed the 2015 ABS consensus (1mm for invasive and 1mm for DCIS), this would have avoided surgery in 70 cases resulting in a new re-excision rate 14.8% (p=0.01) (Figure 2). 65% patients returned to theatre because of disease present at margin(s) while 35% were due to proximity of cancer to specimen margin.

DISCUSSION

This was the first prospective national collaborative study of margin policy in the UK and Ireland following the publication of the SSO-ASTRO and ABS guidelines. This study involved 147 investigators in 79 units contributing data on 2858 patients and describing the practice of 272 breast surgeons.

Our study has shown large variation in accepted adequate margin width for BCT, with greater variation seen for DCIS than for invasive disease. Despite level 1 evidence, only 4 units followed the ASCO consensus guideline for invasive disease. The dedicated session on excision margins at the 2015 ABS annual conference and its large membership are likely factors contributing to the relatively high percentage of units (49%) following its consensus guidance. The observed variation in practice is surprising given the strength of evidence used to support the new SSS-ASTRO guidelines and the historical willingness of the breast surgical community to adopt evidenced based practice. This variation contrasts with marked uniformity in the approach to localising non-palpable lesions with 99% of units using radiologically inserted guidewires and 96% of units favouring specimen X-ray for intraoperative margin assessment. A randomized controlled trial of cavity shave margins in breast cancer showed a reduction in re-excision rates from 38% to 19% with no reduction in patient perceived cosmetic outcome{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1056/NEJMoa1504473", "ISBN" : "1533-4406 (Electronic)\r0028-4793 (Linking)", "ISSN" : "0028-4793", "PMID" : "26028131", "abstract" : "In a study involving women undergoing breast-conserving therapy, the group that had the cavity of tumor resection shaved had a significantly lower rate of positive margins than the no-shave group (19% vs. 34%). Half as many such patients required second surgery for margin clearance.", "author" : [{ "dropping-particle" : "", "family" : "Chagpar", "given" : "Anees B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Killelea", "given" : "Brigid K.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tsangaris", "given" : "Theodore N.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Butler", "given" : "Meghan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stavris", "given" :

"Karen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Li", "given" : "Fangyong", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Yao", "given" : "Xiaopan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bossuyt", "given" : "Veerle", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Harigopal", "given" : "Malini", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lannin", "given" : "Donald R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pusztai", "given" : "Lajos", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Horowitz", "given" : "Nina R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "New England Journal of Medicine", "id" : "ITEM-1", "issue" : "6", "issued" : { "date-parts" : [["2015"]] }, "page" : "503-510", "title" : "A Randomized, Controlled Trial of Cavity Shave Margins in Breast Cancer", "type" : "article-journal", "volume" : "373" }, "uris" : ["http://www.mendeley.com/documents/?uuid=bad6cc48-834c-4150-91e7-635215b61ef6"] }], "mendeley" : { "formattedCitation" : "³⁸", "plainTextFormattedCitation" : "38", "previouslyFormattedCitation" : "³⁸" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. However, our study shows a low uptake of routine 4 cavity shave margins with only 24 surgeons incorporating this into their standard practice. Improving uniformity in margin practice would be in line with “Getting It Right First Time”, NHS Improvement’s national programme to address variation in healthcare provision**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "URL" : "https://improvement.nhs.uk/news-alerts/getting-it-right-first-time-recruits-new-clinical-leads/#h2-current-specialities-and-clinical-leads", "id" : "ITEM-1", "issued" : { "date-parts" : [["0"]] }, "title" : "Getting it Right First Time", "type" : "webpage" }, "uris" : ["http://www.mendeley.com/documents/?uuid=7be98ea1-ec33-4b1c-b166-3830cce7ec31"] }], "mendeley" : { "formattedCitation" : "³⁹", "plainTextFormattedCitation" : "39", "previouslyFormattedCitation" : "³⁹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Ideally this should be achieved by the publication of national guidelines backed by level 1 evidence and the elimination of separate regional guidelines.

The national re-excision rate identified by our prospective study was 17.2% and is similar to retrospective data for England{ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1136/bmj.e4505", "ISBN" : "1756-1833 (Electronic)\\r0959-535X (Linking)", "ISSN" : "1756-1833", "PMID" : "22791786", "abstract" : "OBJECTIVES: To examine whether rate of reoperation after breast conserving surgery is associated with patients' characteristics and investigate whether reoperation rates vary among English NHS trusts.\\n\\nDESIGN: Cohort study using patient level data from hospital episode statistics.\\n\\nSETTING: English NHS trusts.\\n\\nPARTICIPANTS: Adult women who had breast conserving surgery between 1 April 2005 and 31 March 2008.\\n\\nMAIN OUTCOME MEASURE: Reoperation rates after primary breast conserving surgery within 3 months, adjusted using logistic regression for tumour type, age, comorbidity, and socioeconomic deprivation. Tumours were grouped by whether a carcinoma in situ component was coded at the time of the primary breast conserving surgery.\\n\\nRESULTS: 55,297 women had primary breast conserving surgery in 156 NHS trusts during the three year period. 11,032 (20.0%, 95% confidence interval 19.6% to 20.3%) women had at least one reoperation. 10,212 (18.5%, 18.2% to 18.8%) had one reoperation only; of these, 5943 (10.7%, 10.5% to 11.0%) had another breast conserving procedure and 4269 (7.7%, 7.5% to 7.9%) had a mastectomy. Of the 45,793 women with isolated invasive disease, 8229 (18.0%) had at least one reoperation. In comparison, 2803 (29.5%) of the 9504 women with carcinoma in situ had at least one reoperation (adjusted odds ratio 1.9, 95% confidence interval 1.8 to 2.0). Substantial differences were found in the adjusted reoperation rates among the NHS trusts (10th and 90th centiles 12.2% and 30.2%).\\n\\nCONCLUSION: One in five women who had breast conserving surgery in England had a reoperation. Reoperation was nearly twice as likely when the tumour had a carcinoma in situ component coded. Women should be informed of this reoperation risk when deciding on the type of surgical treatment of their breast cancer.", "author" : [{ "dropping-particle" : "", "family" : "Jeevan", "given" : "R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cromwell", "given" : "D. A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Trivella", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lawrence", "given" : "G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kearins", "given" : "O.", "non-dropping-particle" : "",

"parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pereira", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sheppard", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Caddy", "given" : "C. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Meulen", "given" : "J. H. P.", "non-dropping-particle" : "van der", "parse-names" : false, "suffix" : "" }], "container-title" : "BMJ", "id" : "ITEM-1", "issue" : "jul12 2", "issued" : { "date-parts" : [["2012"]] }, "page" : "e4505-e4505", "title" : "Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics", "type" : "article-journal", "volume" : "345" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8ab50923-cc06-49de-af70-cc578d25b7c4"] }], "mendeley" : { "formattedCitation" : "³²", "plainTextFormattedCitation" : "32", "previouslyFormattedCitation" : "³²" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. We have found wide variation in re-excision rates across units with some units reporting re-excision rates up to 40%. Analysis of infrastructure data found that the only variable associated with an increased rate of margin re-excision in participating units was having more than one trainee. This is an interesting finding and may reflect the possible dilution of supervision in these units particularly when trainees jointly perform operations with minimal consultant input. Data were also analysed to determine whether local margin policies affect re-excision rates. Adoption of the SSO-ASTRO consensus guideline in invasive disease has been shown to reduce re-excision rates both in the USA**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1245/s10434-016-5516-5", "ISSN" : "1068-9265", "abstract" : "BACKGROUND: In February 2014 , the Society of Surgical Oncology and the American Society for Radiation Oncology released guidelines standardizing a negative margin after breast-conserving surgery (BCS) as \"no ink on tumor\" in patients with early-stage invasive cancer. We sought to determine whether reexcision rates after initial BCS decreased after guideline publication, using the ASBrS MasterySM of Breast Surgery Program. METHODS: Between January 2013 and June 2015, data from the ASBrS MasterySM database was analyzed to determine reexcision rates pre and post guideline publication. Reasons for reexcision were evaluated as were the associations with patient and provider characteristics. Chi square test, Fisher's exact test,

Student's t test, ANOVA, and multivariable logistic regression were used as appropriate. All analyses were performed using Microsoft Excel and SPSS, with p value <0.05 as significant. RESULTS: Among 252 providers, the overall reexcision rate after initial BCS decreased by 3.7 % from 20.2 to 16.5 % (p < 0.001). Notable was a 13.8 % decrease (p < 0.001) in reexcisions being done for close margins. Of the analyzed physician and patient characteristics the majority of subgroups showed decreases between the two time periods; however, only \"Percent Breast Surgery in Practice\" was significant. On adjusted analysis, there were no specific patient factors associated with a reduction in reexcision rates. CONCLUSIONS: Following the SSO-ASTRO \"no ink on tumor\" guideline publication, a reduction in overall reexcision rates and reexcision rates for close margins after initial BCS was observed in the ASBrS MasterySM database. More widespread implementation outside this group of early adopters is anticipated with ongoing dissemination.", "author" : [{ "dropping-particle" : "", "family" : "Schulman", "given" : "Amanda M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mirrielees", "given" : "Jennifer A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Leverson", "given" : "Glen", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Landercasper", "given" : "Jeffrey", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Greenberg", "given" : "Caprice", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wilke", "given" : "Lee G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of Surgical Oncology", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2017"]] }, "page" : "52-58", "title" : "Reexcision Surgery for Breast Cancer: An Analysis of the American Society of Breast Surgeons (ASBrS) MasterySM Database Following the SSO-ASTRO \u201cNo Ink on Tumor\u201d Guidelines", "type" : "article-journal", "volume" : "24" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e8a5bf99-dcc8-4682-86ad-527ed20c7047"] }, { "id" : "ITEM-2", "itemData" : { "author" : [{ "dropping-particle" : "", "family" : "Rosenberger", "given" : "LH", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mamtani", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "S", "given" : "Fuzesi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stempel", "given" : "M", "non-dropping-particle" : "",

"parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Eaton", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morrow", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gemignani", "given" : "ML", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of surgical oncology", "id" : "ITEM-2", "issue" : "10", "issued" : { "date-parts" : [["2016"]] }, "page" : "3239-3246", "title" : "Early Adoption of the SSO-ASTRO Consensus Guidelines on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: Initial Experience from Memorial Sloan Kettering Cancer Center", "type" : "article-journal", "volume" : "23" }, "uris" : ["http://www.mendeley.com/documents/?uuid=be501df6-474d-48d8-87f6-4ae435508149"] }], "mendeley" : { "formattedCitation" : "^{40,41}", "plainTextFormattedCitation" : "40,41", "previouslyFormattedCitation" : "^{40,41}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** and in individual UK breast units**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "author" : [{ "dropping-particle" : "", "family" : "Tang S., Pereira B., May J., Reddy D.", "given" : "Sharma AKS.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "EJSO", "id" : "ITEM-1", "issue" : "S35-S36", "issued" : { "date-parts" : [["2016"]] }, "title" : "Excision margins in breast conservation therapy (BCT) \u2013 The effect of the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) consensus on our practice. EJSO 2016: 42; S35-S36)", "type" : "article-journal", "volume" : "42" }, "uris" : ["http://www.mendeley.com/documents/?uuid=374e7253-5e7b-48db-94b0-2a715dd464d3"] }], "mendeley" : { "formattedCitation" : "⁴²", "plainTextFormattedCitation" : "42", "previouslyFormattedCitation" : "⁴²" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. However, our data show that if all participating breast units applied SSO-ASTRO's guidelines, this would only lower the national re-excision rate from 17.2% to 15.4% (Figure 1). This is similar to the re-excision rate seen at a large unit in the USA following adopting the SSO-ASTRO guidelines (rates fell from 21.4% to 15.1%)**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "author" : [{ "dropping-particle" : "",

"family" : "Rosenberger", "given" : "LH", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mamtani", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "S", "given" : "Fuzesi", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Stempel", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Eaton", "given" : "A", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morrow", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Gemignani", "given" : "ML", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of surgical oncology", "id" : "ITEM-1", "issue" : "10", "issued" : { "date-parts" : [["2016"]] }, "page" : "3239-3246", "title" : "Early Adoption of the SSO-ASTRO Consensus Guidelines on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: Initial Experience from Memorial Sloan Kettering Cancer Center", "type" : "article-journal", "volume" : "23" }, "uris" : ["http://www.mendeley.com/documents/?uuid=be501df6-474d-48d8-87f6-4ae435508149"] }], "mendeley" : { "formattedCitation" : "⁴¹", "plainTextFormattedCitation" : "41", "previouslyFormattedCitation" : "⁴¹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Similarly if all breast units within our study followed the 2015 ABS consensus, this would only lower the re-excision rate to 14.8%. Importantly, further analysis demonstrated that 65% of patients returned to theatre because of disease present at the margin rather than close margins. Consequently simply changing margin definitions will only have a small impact on re-excision rates and other approaches to improve the rate of complete excision should be developed.

Due to variation in breast cancer biology, it is not possible to eliminate the risk of re-excision entirely. Previous studies have shown that only 37% of localized tumours are truly unifocal at mastectomy serial sub-gross sectioning and in 43% of cases tumour was found at more than 2cm from the index lesion**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1002/1097-0142(19850901)56:5<979::AID-CNCR2820560502>3.0.CO;2-N", "ISSN" : "0008-543X", "PMID" : "2990668", "abstract" :

"Breast cancer multifocality was studied in mastectomy specimens by correlated specimen radiography and histologic techniques. The patients chosen for study were comparable to those eligible for breast- conserving surgical therapy. Two study groups, one with 282 invasive cancers (Tl-2) and the other with 32 intraductal cancers, were selected from a group of 399 consecutive cases by omitting patients who were clearly, or very probably, not candidates for breast-conserving surgical therapy according to current trial criteria. Omitted patients included those with clinically and/or radiologically multifocal cancers and patients with tumor extension into the chest wall or skin (7%). Also excluded were the so- called diffuse invasive cancers @%), the clinically and radiologically occult tumors (3%), and the invasive cancers larger than 5 cm (3%). Of the 282 invasive cancers, 105 (37%) showed no tumor foci in the mastectomy specimen around the reference mass. In 56 (20%) tumor foci were present within 2 cm, and in 121 (43%) tumor was found more than 2 cm from the reference tumor. In 75 (27%) the tumor foci beyond 2 cm were histologically noninvasive cancers, and in 46 cases (16%) they contained invasive cancers as well. A comparison between the group with reference tumors less than 2 cm and the group with reference tumors more than 2 cm in size showed no significant difference between the groups in terms of presence or absence of tumor foci or distance of tumor foci from the reference tumor. If the 264 invasive cancers in this series that were 4 cm or less in diameter had been removed with a margin of 3 to 4 cm, 7% to 9% of the patients would have had invasive cancer left in the remaining breast tissue, and 4% to 9% would have had foci of noninvasive cancer left in the remaining breast tissue. On the basis of the data on the distribution of tumor at different distances from the reference tumor, the current study estimates the expected rates of local recurrences after breast- conserving surgical procedures relative to the extensiveness of the excision. The possible impact of postoperative local radiation therapy on the rates of expected local recurrence is discussed. Cancer", "author" : [{ "dropping-particle" : "", "family" : "Roland Holand, MD,\u2019 SOLKE H. J. VELING, MSC, t MARCEL MRAVUNAC, MD5 AND JAN H. C. L. HENDRIKS", "given" : "Md*", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bre", "given" : "", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer", "id" : "ITEM-1", "issued" : { "date-parts" : [["1985"]] }, "page" : "979-990", "title" : "Histologic Multifocality of Tis, T I -2 Breast Carcinomas. implications for Clinical Trials of Breast-Conserving Surgery", "type" : "article-journal", "volume" : "56" }, "uris" : [

"http://www.mendeley.com/documents/?uuid=2ce66c29-353d-46ab-9ffe-94c86d2f98ae"] }], "mendeley" : { "formattedCitation" : "⁴³", "plainTextFormattedCitation" : "43", "previouslyFormattedCitation" : "⁴³" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. This evidence does not, however, support the practice of increasing mastectomy rates because we know adjuvant therapies play an important role in local control and the large RCTs have shown that BCT is equivalent to mastectomy**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1080/02841860801971439", "ISBN" : "0284186080197", "ISSN" : "1651-226X", "PMID" : "18465335", "abstract" : "The main objective of the present study aims at comparing the long-term efficacy of breast conserving surgery (BCS) vs. mastectomy (M) based on a randomized design. The Danish Breast Cancer Cooperative Group (DBCG) conducted the trial (DBCG-82TM) from January 1983 to March 1989 recruiting 1154 patients with invasive breast carcinoma. Follow-up time ended 1(st) May 2006 with a median follow-up time of 19.6 years (time span 17.1-23.3 years). Eligibility criteria included a one-sided, unifocal, primary operable breast carcinoma, patient age below 70 years, probability of satisfactory cosmetic outcome with BCS, and no evidence of disseminated disease. The patients accrued were grouped into three subsets: correctly randomized, suspicion of randomization error, and declining randomization. The main analyses focus on the subgroup of 793 correctly randomized patients representing 70% of the complete series. 10-year recurrence free survival (RFS) and 20-year overall survival (OS) based on intent to treat did not reveal significant differences in outcome between breast conserving surgery vs. mastectomy, p=0.95 and p=0.10, respectively. Including the complete series comprising 1133 eligible patients based on treatment in fact given similarly no significant difference between surgical options could be traced in outcome of 10-year RFS and 20-year OS, p=0.94 and p=0.24, respectively. The pattern of recurrences as a first event in breast conservation vs. mastectomy did not differ significantly irrespective of site, p=0.27. Looking into the type of local relapse, viz., new primaries vs. true recurrences, it appeared that new primaries were significantly associated to BCS, while true recurrences dominated among M treated patients (p<0.001). In conclusion, long-term data indicate that BCS in eligible patients proves as effective as mastectomy both regarding local tumour control, RFS and OS. Local failures as a first event consistent with new primaries are strongly associated with BCS, whereas true

recurrence predominates after mastectomy.", "author" : [{ "dropping-particle" : "", "family" : "Blichert-Toft", "given" : "Mogens", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nielsen", "given" : "Maja", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "D\u00fcring", "given" : "Maria", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "M\u00f8ller", "given" : "Susanne", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Rank", "given" : "Fritz", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Overgaard", "given" : "Marie", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mouridsen", "given" : "Henning T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Acta Oncol", "id" : "ITEM-1", "issue" : "4", "issued" : { "date-parts" : [["2008"]] }, "page" : "672-81", "title" : "Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol.", "type" : "article-journal", "volume" : "47" }, "uris" : ["http://www.mendeley.com/documents/?uuid=10f1a4b0-de08-46ac-9ee8-5a60ccda5b39"] }, { "id" : "ITEM-2", "itemData" : { "ISBN" : "1081-4442 (Print)", "ISSN" : "1081-4442 (Print)", "PMID" : "9072310", "abstract" : "BACKGROUND: The randomized trials comparing breast-conserving therapy (BCT), i.e., surgery and radiation to the breast, with mastectomy in early-stage breast cancer use a variety of protocols. Meta-analysis may assist in understanding the impact of these differences on survival. PURPOSE: To evaluate the possible variations of the relative efficacy of BCT and mastectomy in terms of overall survival according to tumor size, nodal status, and use of adjuvant radiation therapy. METHODS: The most recent published results and, where available, updated patient-level data from randomized controlled trials of BCT and mastectomy for early-stage breast cancer were combined in a meta-analysis using a random effects model. Pooled survival rates and odds ratios were generated according to subgroups of nodal status and tumor size. Five- and 10-year odds ratios were also determined according to adjuvant radiation protocol. RESULTS: The pooled odds ratio comparing 10-year survival for BCT and mastectomy was 0.91. The odds ratios comparing the two treatment regimens were not significant after grouping according to tumor size and nodal status. When more than 50% of node-positive patients in both the mastectomy and BCT arms received adjuvant radiation, both arms had similar survival rates. When less than

50% of node-positive patients in both arms received adjuvant nodal radiation, the odds ratio was 0.69, and patients receiving BCT had a survival advantage. CONCLUSIONS: Patients allocated to BCT have survival rates at least as high as patients allocated to mastectomy. When all protocols were combined, nodal status and tumor size did not significantly alter the relative survival rates. However, under some conditions, particularly for node-positive patients, BCT may confer a relative survival advantage over mastectomy. In particular, mastectomy without adjuvant radiation appears to be inferior to BCT for node-positive patients.", "author" : [{ "dropping-particle" : "", "family" : "Morris", "given" : "A D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morris", "given" : "R D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wilson", "given" : "J F", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "White", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Steinberg", "given" : "S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Okunieff", "given" : "P", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Arriagada", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Le", "given" : "M G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Blichert-Toft", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dongen", "given" : "J A", "non-dropping-particle" : "van", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer J Sci Am", "id" : "ITEM-2", "issued" : { "date-parts" : [["1997"]] }, "page" : "6-12", "title" : "Breast-conserving therapy vs mastectomy in early-stage breast cancer: a meta-analysis of 10-year survival", "type" : "article-journal", "volume" : "3" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ff580f0e-ab26-47da-afff-54249f8c72c0"] }, { "id" : "ITEM-3", "itemData" : { "DOI" : "10.1002/cncr.11580", "ISBN" : "0008-543X (Print)\\n0008-543X (Linking)", "PMID" : "12910512", "abstract" : "BACKGROUND: Between 1979-1987, the National Cancer Institute conducted a randomized, prospective study of mastectomy (MT) versus breast conservation therapy (BCT) in the treatment of patients with early-stage breast carcinoma. After a median potential follow-up of 18.4 years, the authors present the updated results. METHODS: After informed consent was obtained from

each patient, 237 evaluable women with clinical AJCC Stage I and Stage II breast carcinoma were enrolled on an institutionally reviewed protocol and randomly assigned to undergo modified radical MT (116 patients) or BCT (121 patients), which was comprised of lumpectomy, axillary lymph node dissection, and radiation therapy. Negative surgical margins in the lumpectomy arm were not required. The 237 randomized patients were followed for a median potential follow-up of 18.4 years. The primary endpoints were overall survival and disease-free survival. RESULTS: At a median follow-up of 18.4 years, there was no detectable difference with regard to overall survival between patients treated with MT and those treated with BCT (58% vs. 54%; P = 0.67 overall). Twenty-seven women in the BCT arm (22%) experienced an in-breast event. After censoring in-breast events in the BCT arm that were salvaged successfully by MT, disease-free survival also was found to be statistically similar (67% in the MT arm vs. 63% in the BCT arm; P = 0.64 overall). There was no statistically significant difference with regard to contralateral breast carcinoma between the two treatment arms (P = 0.70). CONCLUSIONS: After nearly 20 years of follow-up, there was no detectable difference in overall survival or disease-free survival in patients with early-stage breast carcinoma who were treated with MT compared with those treated with BCT. For BCT patients, long-term in-breast failures continued to occur throughout the duration of follow-up. There was no statistically significant difference in the incidence of contralateral breast carcinoma between the two treatment groups.", "author" : [{ "dropping-particle" : "", "family" : "Poggi", "given" : "M M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Danforth", "given" : "D N", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sciuto", "given" : "L C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Smith", "given" : "S L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Steinberg", "given" : "S M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Liewehr", "given" : "D J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Menard", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lippman", "given" : "M E", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lichter", "given" : "A S", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" :

"Altemus", "given" : "R M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Cancer", "id" : "ITEM-3", "issue" : "4", "issued" : { "date-parts" : [["2003"]] }, "page" : "697-702", "title" : "Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial", "type" : "article-journal", "volume" : "98" }, "uris" : ["http://www.mendeley.com/documents/?uuid=a2d62752-04af-41f2-8a24-ae13d9936028"] }, { "id" : "ITEM-4", "itemData" : { "DOI" : "10.1056/NEJMoa020989", "ISBN" : "1533-4406 (Electronic)\\n0028-4793 (Linking)", "ISSN" : "1533-4406", "PMID" : "12393819", "abstract" : "BACKGROUND We conducted 20 years of follow-up of women enrolled in a randomized trial to compare the efficacy of radical (Halsted) mastectomy with that of breast-conserving surgery. METHODS From 1973 to 1980, 701 women with breast cancers measuring no more than 2 cm in diameter were randomly assigned to undergo radical mastectomy (349 patients) or breast-conserving surgery (quadrantectomy) followed by radiotherapy to the ipsilateral mammary tissue (352 patients). After 1976, patients in both groups who had positive axillary nodes also received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. RESULTS Thirty women in the group that underwent breast-conserving therapy had a recurrence of tumor in the same breast, whereas eight women in the radical-mastectomy group had local recurrences (P<0.001). The crude cumulative incidence of these events was 8.8 percent and 2.3 percent, respectively, after 20 years. In contrast, there was no significant difference between the two groups in the rates of contralateral-breast carcinomas, distant metastases, or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7 percent in the group that underwent breast-conserving surgery and 41.2 percent in the radical-mastectomy group (P=1.0). The respective rates of death from breast cancer were 26.1 percent and 24.3 percent (P=0.8). CONCLUSIONS The long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy. Breast-conserving surgery is therefore the treatment of choice for women with relatively small breast cancers.", "author" : [{ "dropping-particle" : "", "family" : "Veronesi", "given" : "Umberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cascinelli", "given" : "Natale", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mariani", "given" : "Luigi", "non-dropping-particle" : "", "parse-names" : false,

"suffix" : "" }, { "dropping-particle" : "", "family" : "Greco", "given" : "Marco", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saccozzi", "given" : "Roberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luini", "given" : "Alberto", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Aguilar", "given" : "Marisel", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Marubini", "given" : "Ettore", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "The New England journal of medicine", "id" : "ITEM-4", "issue" : "16", "issued" : { "date-parts" : [["2002"]] }, "page" : "1227-32", "title" : "Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer.", "type" : "article-journal", "volume" : "347" }, "uris" : ["http://www.mendeley.com/documents/?uuid=2411ba6b-9560-48ac-8235-bb3b4011e58f"] }, { "id" : "ITEM-5", "itemData" : { "DOI" : "10.1056/NEJMoa020128", "ISBN" : "1533-4406 (Electronic)\\r0028-4793 (Linking)", "ISSN" : "1533-4406", "PMID" : "12192016", "abstract" : "BACKGROUND: In 1976, we initiated a randomized trial to determine whether lumpectomy with or without radiation therapy was as effective as total mastectomy for the treatment of invasive breast cancer. METHODS: A total of 1851 women for whom follow-up data were available and nodal status was known underwent randomly assigned treatment consisting of total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation. Kaplan-Meier and cumulative-incidence estimates of the outcome were obtained. RESULTS: The cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3 percent in the women who underwent lumpectomy and breast irradiation, as compared with 39.2 percent in the women who underwent lumpectomy without irradiation (P<0.001). No significant differences were observed among the three groups of women with respect to disease-free survival, distant-disease-free survival, or overall survival. The hazard ratio for death among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P=0.51). The hazard ratio for death among the women who underwent lumpectomy followed by breast irradiation, as compared with those who underwent total mastectomy, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P=0.74). Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the hazard ratio for death among the women

who underwent postoperative breast irradiation, as compared with those who did not, was 0.91 (95 percent confidence interval, 0.77 to 1.06; P=0.23). Radiation therapy was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes. CONCLUSIONS: Lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained.", "author" : [{ "dropping-particle" : "", "family" : "Fisher", "given" : "Bernard", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Anderson", "given" : "Stewart", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bryant", "given" : "John", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Margolese", "given" : "Richard G", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Deutsch", "given" : "Melvin", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Fisher", "given" : "Edwin R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jeong", "given" : "Jong-Hyeon", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Wolmark", "given" : "Norman", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "N Engl J Med", "id" : "ITEM-5", "issue" : "16", "issued" : { "date-parts" : [["2002"]] }, "page" : "1233-1241", "title" : "Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer", "type" : "article-journal", "volume" : "347" }, "uris" : ["http://www.mendeley.com/documents/?uuid=929981ba-e9f9-4d35-aef7-9f7a173f6a69"] }, { "id" : "ITEM-6", "itemData" : { "ISBN" : "0027-8874", "ISSN" : "0027-8874", "PMID" : "10904087", "abstract" : "BACKGROUND: Breast-conserving therapy (BCT) has been shown to be as effective as mastectomy in the treatment of tumors 2 cm or smaller. However, evidence of its efficacy, over the long term, in patients with tumors larger than 2 cm is limited. From May 1980 to May 1986, the European Organization for Research and Treatment of Cancer carried out a randomized, multicenter trial comparing BCT with modified radical mastectomy for patients with tumors up to 5 cm. In this analysis, we investigated whether the treatments resulted in different overall survival, time to distant

metastasis, or time to locoregional recurrence. METHODS: Of 868 eligible breast cancer patients randomly assigned to the BCT arm or to the modified radical mastectomy arm, 80% had a tumor of 2.1-5 cm. BCT comprised lumpectomy with an attempted margin of 1 cm of healthy tissue and complete axillary clearance, followed by radiotherapy to the breast and a supplementary dose to the tumor bed. The median follow-up was 13.4 years. All P values are two-sided. RESULTS: At 10 years, there was no difference between the two groups in overall survival (66% for the mastectomy patients and 65% for the BCT patients; P =.11) or in their distant metastasis-free rates (66% for the mastectomy patients and 61% for the BCT patients; P =.24). The rate of locoregional recurrence (occurring before or at the same time as distant metastasis) at 10 years did show a statistically significant difference (12% of the mastectomy and 20% of the BCT patients; P =. 01). CONCLUSIONS: BCT and mastectomy demonstrate similar survival rates in a trial in which the great majority of the patients had stage II breast cancer Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial\\nEnglish 200012. Entry Week: 2000121", "author" : [{ "dropping-particle" : "", "family" : "Dongen", "given" : "J A", "non-dropping-particle" : "van", "parse-names" : false, "suffix" : "" }], "container-title" : "Journal of the National Cancer Institute", "id" : "ITEM-6", "issue" : "14", "issued" : { "date-parts" : [["2000"]] }, "page" : "1143-1150", "title" : "Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European organization for research and treatment of cancer 10801 trial 4606", "type" : "article-journal", "volume" : "92" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ac505db9-c427-4f82-a7d1-35034d10f8f3"] }], "mendeley" : { "formattedCitation" : "^{12,13,15\u201318}", "plainTextFormattedCitation" : "12,13,15\u201318", "previouslyFormattedCitation" : "^{12,13,15\u201318}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Nor should we go down the route of excising larger volumes of tissue as this will increase the risk of poor cosmetic outcomes and we have already discussed that wide margins are not necessary for local control**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1245/s10434-014-3480-5", "ISBN" : "1068-9265", "ISSN" : "1068-9265", "PMID" : "24473640", "abstract" : "Purpose: There is no consensus on what constitutes adequate negative margins in breast-conserving therapy (BCT). We systematically review the evidence on surgical margins in BCT for invasive breast cancer to

support the development of clinical guidelines. Methods: Study-level meta-analysis of studies reporting local recurrence (LR) data relative to final microscopic margin status and the threshold distance for negative margins. LR proportion was modeled using random-effects logistic meta-regression. Results: Based on 33 studies (LR in 1,506 of 28,162), the odds of LR were associated with margin status [model 1: odds ratio (OR) 1.96 for positive/close vs negative; model 2: OR 1.74 for close vs. negative, 2.44 for positive vs. negative; (P < 0.001 both models)] but not with margin distance [model 1: >0 mm vs. 1 mm (referent) vs. 2 mm vs. 5 mm (P = 0.12); and model 2: 1 mm (referent) vs. 2 mm vs. 5 mm (P = 0.90)], adjusting for study median follow-up time. There was little to no statistical evidence that the odds of LR decreased as the distance for declaring negative margins increased, adjusting for follow-up time [model 1: 1 mm (OR 1.0, referent), 2 mm (OR 0.95), 5 mm (OR 0.65), P = 0.21 for trend; and model 2: 1 mm (OR 1.0, referent), 2 mm (OR 0.91), 5 mm (OR 0.77), P = 0.58 for trend]. Adjustment for covariates, such as use of endocrine therapy or median-year of recruitment, did not change the findings. Conclusions: Meta-analysis confirms that negative margins reduce the odds of LR; however, increasing the distance for defining negative margins is not significantly associated with reduced odds of LR, allowing for follow-up time. Adoption of wider relative to narrower margin widths to declare negative margins is unlikely to have a substantial additional benefit for long-term local control in BCT. \u00a9 2014 Society of Surgical Oncology.", "author" : [{ "dropping-particle" : "", "family" : "Houssami", "given" : "Nehmat", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Macaskill", "given" : "Petra", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Luke Marinovich", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Morrow", "given" : "Monica", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of Surgical Oncology", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2014"]] }, "page" : "717-730", "title" : "The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis", "type" : "article-journal", "volume" : "21" }, "uris" : ["http://www.mendeley.com/documents/?uuid=db62836c-3d64-49df-8f72-aa33c7d56cff"] }], "mendeley" : { "formattedCitation" : "²⁶", "plainTextFormattedCitation" : "26", "previouslyFormattedCitation" : "²⁶" }, "properties" : { "noteIndex" : 0 },

"schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Instead, complete excision rates should be improved by better identification of patients who are at increased risk of margin involvement (e.g. those with DCIS**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1001/jamasurg.2016.4751", "ISSN" : "2168-6254", "abstract" : "<h3>Importance</h3> New techniques for preoperative localization of nonpalpable breast lesions may decrease the reoperation rate in breast-conserving surgery (BCS) compared with rates after surgery with the standard wire-guided localization. However, a valid reoperation rate for this procedure needs to be established for comparison, as previous studies on this procedure include a variety of malignant and benign breast lesions. <h3>Objectives</h3> To determine the reoperation rate after wire-guided BCS in patients with histologically verified nonpalpable invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS) and to examine whether the risk of reoperation is associated with DCIS or histologic type of the IBC. <h3>Design, Setting, and Participants</h3> This nationwide study including women with histologically verified IBC or DCIS having wire-guided BCS performed between January 1, 2010, and December 31, 2013, used data from the Danish National Patient Registry that were cross-checked with the Danish Breast Cancer Group database and the Danish Pathology Register. <h3>Main Outcomes and Measures</h3> Reoperation rate after wire-guided BCS in patients with IBC or DCIS. <h3>Results</h3> Wire-guided BCS was performed in 4118 women (mean [SD] age, 60.9 [8.7] years). A total of 725 patients (17.6%) underwent a reoperation: 593 were reexcisions (14.4%) and 132 were mastectomies (3.2%). Significantly more patients with DCIS (271 of 727 [37.3%]) than with IBC (454 of 3391 [13.4%]) underwent a reoperation (adjusted odds ratio, 3.82; 95% CI, 3.19-4.58;P\u2009<\u2009.001). After the first reexcision, positive margins were still present in 97 patients (16.4%). The risk of repeated positive margins was significantly higher in patients with DCIS vs those with IBC (unadjusted odds ratio, 2.21; 95% CI, 1.42-3.43;P\u2009<\u2009.001). The risk of reoperation was significantly increased in patients with lobular carcinoma vs those with ductal carcinoma (adjusted odds ratio, 1.44; 95% CI 1.06-1.95;P\u2009=\u2009.02). A total of 202 patients (4.9%) had a subsequent completion mastectomy, but no difference was found in the type of reoperation between patients with DCIS and those with IBC. <h3>Conclusions and Relevance</h3> A lower reoperation rate after wire-

guided BCS was found in this study than those shown in previous studies. However, the risk of reoperation in patients with DCIS was 3 times higher than in those with IBC. The widespread use of m\u2026", "author" : [{ "dropping-particle" : "", "family" : "Langhans", "given" : "Linnea", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jensen", "given" : "Maj-Britt", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Talman", "given" : "Maj-Lis M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Vejborg", "given" : "Ilse", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kroman", "given" : "Niels", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Tvedskov", "given" : "Tove F.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "JAMA Surgery", "id" : "ITEM-1", "issued" : { "date-parts" : [["2016"]] }, "title" : "Reoperation Rates in Ductal Carcinoma In Situ vs Invasive Breast Cancer After Wire-Guided Breast-Conserving Surgery", "type" : "article-journal" }, "uris" : ["http://www.mendeley.com/documents/?uuid=de5223f4-73be-4b82-ae13-59bfeae7d55d"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.1136/bmj.e4505", "ISBN" : "1756-1833 (Electronic)\\r0959-535X (Linking)", "ISSN" : "1756-1833", "PMID" : "22791786", "abstract" : "OBJECTIVES: To examine whether rate of reoperation after breast conserving surgery is associated with patients' characteristics and investigate whether reoperation rates vary among English NHS trusts.\\n\\nDESIGN: Cohort study using patient level data from hospital episode statistics.\\n\\nSETTING: English NHS trusts.\\n\\nPARTICIPANTS: Adult women who had breast conserving surgery between 1 April 2005 and 31 March 2008.\\n\\nMAIN OUTCOME MEASURE: Reoperation rates after primary breast conserving surgery within 3 months, adjusted using logistic regression for tumour type, age, comorbidity, and socioeconomic deprivation. Tumours were grouped by whether a carcinoma in situ component was coded at the time of the primary breast conserving surgery.\\n\\nRESULTS: 55,297 women had primary breast conserving surgery in 156 NHS trusts during the three year period. 11,032 (20.0%, 95% confidence interval 19.6% to 20.3%) women had at least one reoperation. 10,212 (18.5%, 18.2% to 18.8%) had one reoperation only; of these, 5943 (10.7%, 10.5% to 11.0%) had another breast conserving procedure and 4269 (7.7%, 7.5% to 7.9%) had a mastectomy. Of the 45,793 women with isolated invasive disease, 8229 (18.0%) had at least one reoperation. In comparison, 2803 (29.5%) of the 9504 women with

carcinoma in situ had at least one reoperation (adjusted odds ratio 1.9, 95% confidence interval 1.8 to 2.0). Substantial differences were found in the adjusted reoperation rates among the NHS trusts (10th and 90th centiles 12.2% and 30.2%).\\n\\nCONCLUSION: One in five women who had breast conserving surgery in England had a reoperation. Reoperation was nearly twice as likely when the tumour had a carcinoma in situ component coded. Women should be informed of this reoperation risk when deciding on the type of surgical treatment of their breast cancer.", "author" : [{ "dropping-particle" : "", "family" : "Jeevan", "given" : "R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Cromwell", "given" : "D. A.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Trivella", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lawrence", "given" : "G.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kearins", "given" : "O.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pereira", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sheppard", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Caddy", "given" : "C. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Meulen", "given" : "J. H. P.", "non-dropping-particle" : "van der", "parse-names" : false, "suffix" : "" }], "container-title" : "BMJ", "id" : "ITEM-2", "issue" : "jul12 2", "issued" : { "date-parts" : [["2012"]] }, "page" : "e4505-e4505", "title" : "Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics", "type" : "article-journal", "volume" : "345" }, "uris" : ["http://www.mendeley.com/documents/?uuid=8ab50923-cc06-49de-af70-cc578d25b7c4"] }], "mendeley" : { "formattedCitation" : "^{32,44}", "plainTextFormattedCitation" : "32,44", "previouslyFormattedCitation" : "^{32,44}" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**); optimising pre-operative imaging to improve size estimation because underestimation of tumour size by current imaging techniques is a major factor associated with incomplete excision**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1002/bjs.10126", "ISSN" : "13652168", "PMID" : "27171027",

"abstract" : "BACKGROUND: Completeness of excision is the most important factor influencing local recurrence after breast-conserving surgery (BCS). The aim of this case-control study was to determine factors influencing incomplete excision in patients undergoing BCS.\\n\\nMETHODS: Women with invasive breast cancer treated by BCS between 1 June 2008 and 31 December 2009 were identified from a prospectively collected database in the Edinburgh Breast Unit. The maximum size of the tumour, measured microscopically, was compared with the size estimated before operation by mammography and ultrasound imaging. A multivariable analysis was performed to investigate factors associated with incomplete excision.\\n\\nRESULTS: The cohort comprised 311 women, of whom 193 (62\u00b71 per cent) had a complete (CE group) and 118 (40\u00b77 per cent) an incomplete (IE group) excision. Mammography underestimated tumour size in 75\u00b70 per cent of the IE group compared with 40\u00b77 per cent of the CE group (P\u2009<\u20090\u00b7001). Ultrasound imaging underestimated tumour size in 82\u00b75 per cent of the IE group compared with 56\u00b75 per cent of the CE group (P\u2009<\u20090\u00b7001). The risk of an incomplete excision was greater when mammography or ultrasonography underestimated pathological size: odds ratio (OR) 4\u00b738 (95 per cent c.i. 2\u00b759 to 7\u00b741; P\u2009<\u20090\u00b7001) for mammography, and OR 3\u00b764 (2\u00b703 to 6\u00b754; P\u2009<\u20090\u00b7001) for ultrasound imaging. For every 1-mm underestimation of size by mammography and ultrasonography, the relative odds of incomplete excision rose by 10 and 14 per cent respectively.\\n\\nCONCLUSION: Underestimation of tumour size by current imaging techniques is a major factor associated with incomplete excision in women undergoing BCS.", "author" : [{ "dropping-particle" : "", "family" : "Dixon", "given" : "J. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Newlands", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dodds", "given" : "C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Thomas", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Williams", "given" : "L. J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kunkler", "given" : "I. H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Bing", "given" : "A.", "non-dropping-particle" : "", "parse-names" :

false, "suffix" : "" }, { "dropping-particle" : "", "family" : "MacAskill", "given" : "E. J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "British Journal of Surgery", "id" : "ITEM-1", "issue" : "7", "issued" : { "date-parts" : [["2016"]] }, "page" : "830-838", "title" : "Association between underestimation of tumour size by imaging and incomplete excision in breast-conserving surgery for breast cancer", "type" : "article-journal", "volume" : "103" }, "uris" : ["http://www.mendeley.com/documents/?uuid=6fa04832-e229-4ec5-8a1a-226ef833ee20"] }], "mendeley" : { "formattedCitation" : "⁴⁵", "plainTextFormattedCitation" : "45", "previouslyFormattedCitation" : "⁴⁵" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**; and improving methods of intraoperative margin assessment**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "author" : [{ "dropping-particle" : "", "family" : "Leff", "given" : "DR", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "St John", "given" : "ER", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Takats", "given" : "Z", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "JAMA Surgery", "id" : "ITEM-1", "issued" : { "date-parts" : [["2017"]] }, "title" : "Reducing the margins of error during breast-conserving surgery: Disruptive technologies or traditional disruptions?", "type" : "article-journal", "volume" : "Published " }, "uris" : ["http://www.mendeley.com/documents/?uuid=4ccb16bb-187c-4371-b32a-a8b452e2ebfd"] }], "mendeley" : { "formattedCitation" : "⁴⁶", "plainTextFormattedCitation" : "46", "previouslyFormattedCitation" : "⁴⁶" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. The current standard for intraoperative margin assessment using specimen X-ray suffers from poor pooled diagnostic accuracy**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1097/SLA.0000000000001897", "ISBN" : "0000000000", "ISSN" : "0003-4932", "PMID" : "27429028", "abstract" : "Objective: The aim of this study was to conduct a systematic review and meta-analysis to clarify the diagnostic accuracy of intraoperative breast margin assessment (IMA) techniques against which the performance of emerging IMA technologies may be compared. Summary of Background Data: IMA techniques have failed to penetrate routine practice due to limitations, including slow reporting times, technical demands, and

logistics. Emerging IMA technologies are being developed to reduce positive margin and re-excision rates and will be compared with the diagnostic accuracy of existing techniques. Method: Studies were identified using electronic bibliographic searches up to January 2016. MESH terms and all-field search terms included ''Breast Cancer \u00c3 '' AND ''Intraoperative \u00c3 '' AND ''Margin \u00c3 .'' Only clinical studies with raw diagnostic accuracy data as compared with final permanent section histopathology were included. A bivariate model for diagnostic meta-analysis was used to attain overall pooled sensitivity and specificity. Results: Eight hundred thirty-eight unique studies revealed 35 studies for meta-analysis. Pooled sensitivity (Sens), specificity (Spec), and area under the receiver operating characteristic curve (AUROC) values were calculated per group (Sens, Spec, AUROC): frozen section \u00bc 86%, 96%, 0.96 (n \u00bc 9); cytology \u00bc 91%, 95%, 0.98 (n \u00bc 11); intraoperative ultrasound \u00bc 59%, 81%, 0.78 (n \u00bc 4); specimen radiography \u00bc 53%, 84%, 0.73 (n \u00bc 9); optical spectroscopy \u00bc 85%, 87%, 0.88 (n \u00bc 3). Conclusions: Pooled data suggest that frozen section and cytology have the greatest diagnostic accuracy. However, these methods are resource intensive", "author" : [{ "dropping-particle" : "", "family" : "St John", "given" : "Edward Robert", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Al-Khudairi", "given" : "Rashed", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Ashrafian", "given" : "Hutan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Athanasiou", "given" : "Thanos", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Takats", "given" : "Zoltan", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hadjiminas", "given" : "Dimitri John", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Darzi", "given" : "Ara", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Leff", "given" : "Daniel Richard", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Annals of Surgery", "id" : "ITEM-1", "issue" : "2", "issued" : { "date-parts" : [["2017"]] }, "page" : "300-310", "title" : "Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery", "type" : "article-journal", "volume" : "265" }, "uris" : ["http://www.mendeley.com/documents/?uuid=b54891dc-0a03-402d-9837-2decd15f5f66"] }], "mendeley" : { "formattedCitation" : "⁴⁷",

"plainTextFormattedCitation" : "47", "previouslyFormattedCitation" : "⁴⁷" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**. Extremely low re-excision rates (3.6%) have been shown when intra-operative frozen section and imprint cytology of specimen margins are employed**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.surg.2014.03.025", "ISSN" : "00396060", "abstract" : "BACKGROUND\\nReoperation for positive margins after lumpectomy for breast cancer is common. Intraoperative frozen section (FS) margin analysis permits immediate re-excision, avoiding reoperation. The aim of this study was to compare reoperation rates between an institution using routine FS analysis of all margins and the National Surgical Quality Improvement Program (NSQIP) data. \\n\\nMETHODS\\nWe designed a retrospective cohort analysis comparing a FS single institution\u2019s NSQIP data to the national NSQIP data from 2006-2010. Women undergoing lumpectomy for cancer were identified (N=24,217) and reoperation rates were compared using chi-square analyses and multivariable logistic regression. During this time period NSQIP did not differentiate between reoperations for complications or oncologic reasons. Reoperation rates for mastectomy patients (N=21,734) and lumpectomy patients without cancer (N=2,777) over the same time period were analyzed as controls, as reoperations following these procedures likely would be for reasons other than positive margins. \\n\\nRESULTS\\nThe 30-day reoperation rate after lumpectomy for cancer was higher nationally than at the FS institution (13.2% vs 3.6%, p<0.001). Multivariable analysis showed that patients in the national NSQIP data set were over four times as likely to undergo reoperation as those at the FS institution\u2019s (OR 4.19). The reoperation rates were similar between the two, both for patients undergoing mastectomy (4.7% vs 4.5%, p=0.84) and those undergoing lumpectomy for benign diagnosis (2.9% vs 5.9%, p=0.39). \\n\\nCONCLUSIONS\\nIntraoperative FS margin analysis decreases the number of reoperations for patients undergoing breast conservation for breast cancer. This technique has significant implications for patient satisfaction and cost of care.", "author" : [{ "dropping-particle" : "", "family" : "Boughey", "given" : "Judy C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Hieken", "given" : "Tina J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Jakub", "given" : "James W.", "non-dropping-particle" : "", "parse-

names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Degnim", "given" : "Amy C.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Grant", "given" : "Clive S.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Farley", "given" : "David R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Thomsen", "given" : "Kristine M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Osborn", "given" : "John B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Keeney", "given" : "Gary L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Habermann", "given" : "Elizabeth B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Surgery", "id" : "ITEM-1", "issued" : { "date-parts" : [["2014"]] }, "title" : "Impact of Frozen Section Margin Analysis on Reoperation Rates in Women Undergoing Lumpectomy for Breast Cancer: Evaluation of the NSQIP data", "type" : "article-journal" }, "uris" : ["http://www.mendeley.com/documents/?uuid=69ed7e2c-d8f0-4857-9040-c34a8a84256c"] }], "mendeley" : { "formattedCitation" : "⁴⁸", "plainTextFormattedCitation" : "48", "previouslyFormattedCitation" : "⁴⁸" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** but low uptake of this approach is likely explained by the significant associated logistical and cost implications. The development of new real-time technologies for margin assessment, such as MarginProbe**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1586/erd.13.5", "ISSN" : "1745-2422", "PMID" : "23668703", "abstract" : "In breast conserving surgery, the tumor should be removed with a clean margin, a rim of healthy tissue surrounding. Failure to achieve clean margins in the initial surgery results in a re-excision procedure. Re-excision rates are reported as being 11-46% for invasive carcinoma and ductal carcinoma in situ (DCIS). Re-excisions can have negative consequences such as increased postoperative infections, negative impact on cosmesis, patient anxiety and increased medical costs. Therefore, the surgical margin of invasive and intraductal (DCIS) breast tissue is a subject of intense discussion. Different options for intraoperative assessment are available, but all in all, they are unsatisfying. Frozen section margin examination is possible but is time consuming and restricted to the assessment of invasive carcinoma. In the case of DCIS, there is no procedure for

intraoperative margin assessment. Thus, a solution for efficient intraoperative surgical margin assessment is needed. For this purpose, an innovative, real-time, intraoperative margin-assessment device (MarginProbe, Dune Medical Devices, Caesarea, Israel) was designed, and recent published clinical data reported a reduction of re-excisions by more than 50%.", "author" : [{ "dropping-particle" : "", "family" : "Thill", "given" : "Marc", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Expert review of medical devices", "id" : "ITEM-1", "issue" : "3", "issued" : { "date-parts" : [["2013"]] }, "page" : "301-15", "title" : "MarginProbe: intraoperative margin assessment during breast conserving surgery by using radiofrequency spectroscopy.", "type" : "article-journal", "volume" : "10" }, "uris" : ["http://www.mendeley.com/documents/?uuid=f030f22b-a633-442e-867a-4dfb86152456"] }], "mendeley" : { "formattedCitation" : "⁴⁹", "plainTextFormattedCitation" : "49", "previouslyFormattedCitation" : "⁴⁹" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}**, ClearEdge**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "http://doi.org/10.1016/j.ejso.2016.07.141", "ISSN" : "0748-7983", "abstract" : "AbstractIntroduction Breast conserving surgery (BCS) aims to remove a breast cancer completely and obtain clear margins. Complete excision is essential to reduce the risk of local recurrence. The ClearEdge\u2122 (CE) imaging device examines margins of excised breast tissue intra-operatively. The aim of this study was to investigate the potential of the device in detecting margin involvement in patients having BCS. Methods In Phase-1 58 patients underwent BCS and had 334 margins assessed by the device. In Phase-2 the device was used in 63 patients having BCS and 335 margins were assessed. Patients with margins considered close or involved by the CE device were re-excised. Results The margin assessment accuracies in Phase-1 and Phase-2 compared to permanent section pathology were very similar: sensitivity (84.3% and 87.3%), specificity (81.9% and 75.6%), positive predictive value (67.2% and 63.6%), and negative predictive value (92.2% and 92.4%). The false positive rate (18.1% and 24.4%) and false negative rate (15.7% and 12.7%) were low in both phases. In Phase-2 re-excision rate was 37%, but in the 54 where the CE device was used appropriately the re-excision rate was 17%. Had all surgeons interpreted all images appropriately and re-excised margins detected as abnormal by the device in Phase-2 then the re-excision rate would have been 7%. Conclusion This study shows that the CE device

has potential to reduce re-excision after BCS and further randomized studies of its value are warranted.", "author" : [{ "dropping-particle" : "", "family" : "Dixon", "given" : "J M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Renshaw", "given" : "L", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Young", "given" : "O", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kulkarni", "given" : "D", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Saleem", "given" : "T", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sarfaty", "given" : "M", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sreenivasan", "given" : "R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kusnick", "given" : "C", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Thomas", "given" : "J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Williams", "given" : "L J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "European Journal of Surgical Oncology (EJSO)", "id" : "ITEM-1", "issue" : "12", "issued" : { "date-parts" : [["2016", "12"]] }, "page" : "1834-1840", "title" : "Intra-operative assessment of excised breast tumour margins using ClearEdge imaging device", "type" : "article-journal", "volume" : "42" }, "uris" : ["http://www.mendeley.com/documents/?uuid=cf2ff7e1-8287-4973-9a54-8868f071b4d2"] }], "mendeley" : { "formattedCitation" : "⁵⁰", "plainTextFormattedCitation" : "50", "previouslyFormattedCitation" : "⁵⁰" }, "properties" : { "noteIndex" : 0 }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }**}** and iKnife**{**ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1126/scitranslmed.3005623", "ISBN" : "1946-6242 (Electronic)\\r1946-6234 (Linking)", "ISSN" : "1946-6234", "PMID" : "23863833", "abstract" : "Rapid evaporative ionization mass spectrometry (REIMS) is an emerging technique that allows near-real-time characterization of human tissue in vivo by analysis of the aerosol (\"smoke\") released during electrosurgical dissection. The coupling of REIMS technology with electrosurgery for tissue diagnostics is known as the intelligent knife (iKnife). This study aimed to validate the technique by applying it to the analysis of fresh human tissue samples ex vivo and to demonstrate the translation to real-time use in

vivo in a surgical environment. A variety of tissue samples from 302 patients were analyzed in the laboratory, resulting in 1624 cancerous and 1309 noncancerous database entries. The technology was then transferred to the operating theater, where the device was coupled to existing electrosurgical equipment to collect data during a total of 81 resections. Mass spectrometric data were analyzed using multivariate statistical methods, including principal components analysis (PCA) and linear discriminant analysis (LDA), and a spectral identification algorithm using a similar approach was implemented. The REIMS approach differentiated accurately between distinct histological and histopathological tissue types, with malignant tissues yielding chemical characteristics specific to their histopathological subtypes. Tissue identification via intraoperative REIMS matched the postoperative histological diagnosis in 100% (all 81) of the cases studied. The mass spectra reflected lipidomic profiles that varied between distinct histological tumor types and also between primary and metastatic tumors. Thus, in addition to real-time diagnostic information, the spectra provided additional information on divergent tumor biochemistry that may have mechanistic importance in cancer.", "author" : [{ "dropping-particle" : "", "family" : "Balog", "given" : "J\u00falia", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Sasi-Szabo", "given" : "L.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Kinross", "given" : "James", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lewis", "given" : "Matthew R", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Muirhead", "given" : "Laura J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Veselkov", "given" : "Kirill", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Mirnezami", "given" : "Reza", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dezso", "given" : "B.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Damjanovich", "given" : "L\u00e1szl\u00f3", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Darzi", "given" : "Ara", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Nicholson", "given" : "Jeremy K", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Takats", "given" : "Z.", "non-dropping-particle" : "", "parse-names" :

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FUNDING

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REFERENCES

{ADDIN Mendeley Bibliography CSL_BIBLIOGRAPHY }

Tables and figures

*Table { SEQ Table * ARABIC }. Characteristics of breast units surveyed*

	Mean	(SD)	Median	IQR
Number of consultant surgeons in unit	3.4	1.5	3	2-4
Number of specialty doctors in unit	1.4	1.2	1	1-2
Number of trainees (ST3+) in unit	1.7	1.4	1	1-2
Breast cancers treated per year	372	164	342	250-450
Breast conserving surgery (% cancers)	66.9%	9.5%	70%	60%-75%

*It was possible for centres to choose multiple guidelines being followed.
SD: standard deviation; IQR: Interquartile range; ST3+ : Specialty Registrar year 3 and above

*Table { SEQ Table * ARABIC }. Guidelines breast units follow for margin re-excision*

Guideline	Number of sites	%	95% CI
ABS (2015)	38	48.1%	37.3%-59.0%
Local MDT consensus	31	39.2%	29.0%-50.2%
NICE (2009)	17	21.5%	13.6%-31.5%
Regional	13	16.5%	9.6%-25.8%
ASCO (2014)	3	3.8%	1.1%-9.8%
Total	**102***	**129.1%**	

*It was possible for centres to choose multiple guidelines being followed.
CI: confidence interval (Jeffreys); ABS: Association of Breast Surgeons (UK); MDT: Multi-disciplinary team meeting; NICE:

Table 3. MDT standards for an adequate margin in invasive disease

Standard	Number of sites	%	95% CI
No ink on tumour	11	13.9%	7.6%-22.8%
1mm	61	77.2%	67.1%-85.4%
2mm	6	7.6%	3.2%-15.0%
5mm	1	1.3%	0%-3.1%
Total	**79**	**100%**	

CI: confidence interval (Jeffreys)

Table 4. MDT standards for an adequate margin in DCIS

Standard	Number of sites	%	95% CI

No ink on tumour	4	5.1%	1.7%-11.6%
1mm	42	53.2%	42.2%-63.9%
2mm	30	38.0%	27.9%-49.0%
5mm	3	3.8%	0%-3.1%
Total	**79**	**100%**	

CI: confidence interval (Jeffreys)

Table 5. Methods breast units follow for localisation of nonpalpable lesions

Method	Number of sites	%	95% CI
Wire localisation	78	98.7%	94.2%-99.9%
ROLL	3	3.8%	1.1%-9.8%
Other	1	1.3%	0.1%-5.8%
Total	**82***	**103.8%**	

*It was possible for centres to choose multiple methods being followed.
CI: confidence interval (Jeffreys); ROLL: Radioguided occult lesion localization

Table 6. Methods breast units follow for intra-operative margin assessment

Method	Number of sites	%	95% CI
Specimen X-ray	76	96.2%	90.2%-98.9%
Gross specimen examination	46	58.2%	47.2%-68.6%
MarginProbe	1	1.3%	0.1%-5.8%
Frozen section / Other	0	0%	0%-3.1%
Total	**123***	**155.7%**	

*It was possible for centres to choose multiple methods being followed.
CI: confidence interval (Jeffreys)

Table 7. Breast units' policy for cavity shaves

Method	Number of sites	%	95% CI
After clinical or radiological assessment of the specimen	67	87.0%	78.2%-93.1%
Standard protocol for some surgeons in the unit	6	7.8%	3.3%-15.4%
Standard protocol for all surgeons in the unit	4	5.2%	1.8%-5.9%
No answer	2	2.5%	
Total	**79**	**100%**	

CI: confidence interval (Jeffreys)

Figure 1. Map of the United Kingdom and Ireland showing locations of all participating breast units

Figure 2. Re-excision rates for NHS Trusts

Re-excision rates are presented as a percentage of the total number of WLEs performed by each unit during the study period. Units are listed in ascending order of the number for WLEs performed during the study period. No correlation was found between number of WLEs performed and re-excision rate (p=0.84)

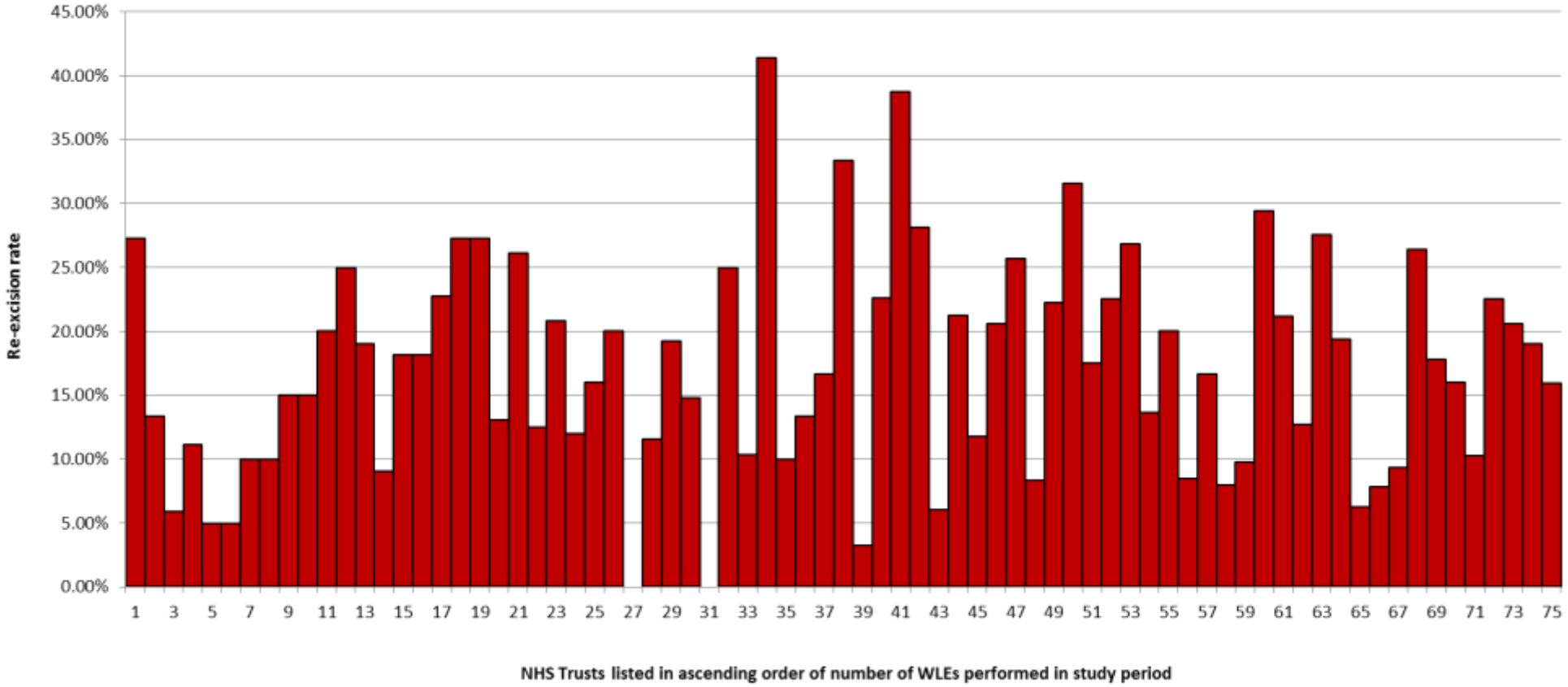
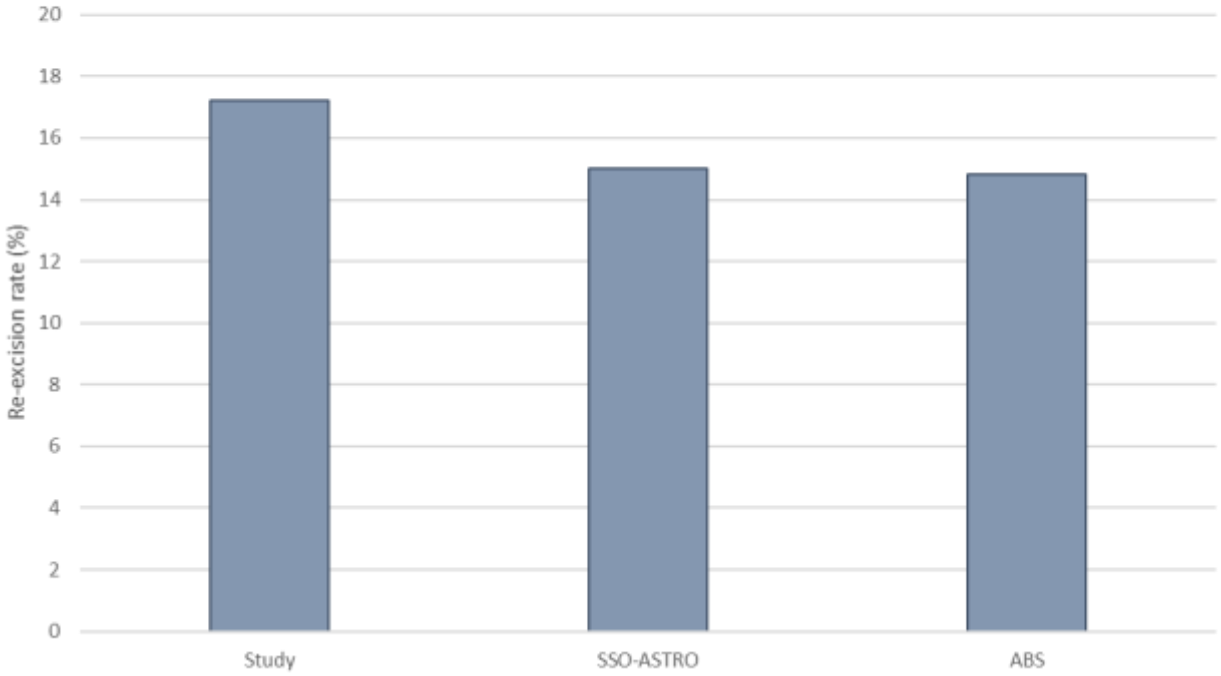


Figure 3. Bar chart showing the current re-excision rate in this study compared to re-excision rates if the SSO-ASTRO consensus guidelines ("no ink on tumour" for invasive carcinoma and 2mm for DCIS) or ABS guideline (1mm for both invasive carcinoma and DCIS) had been applied for all patients.



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